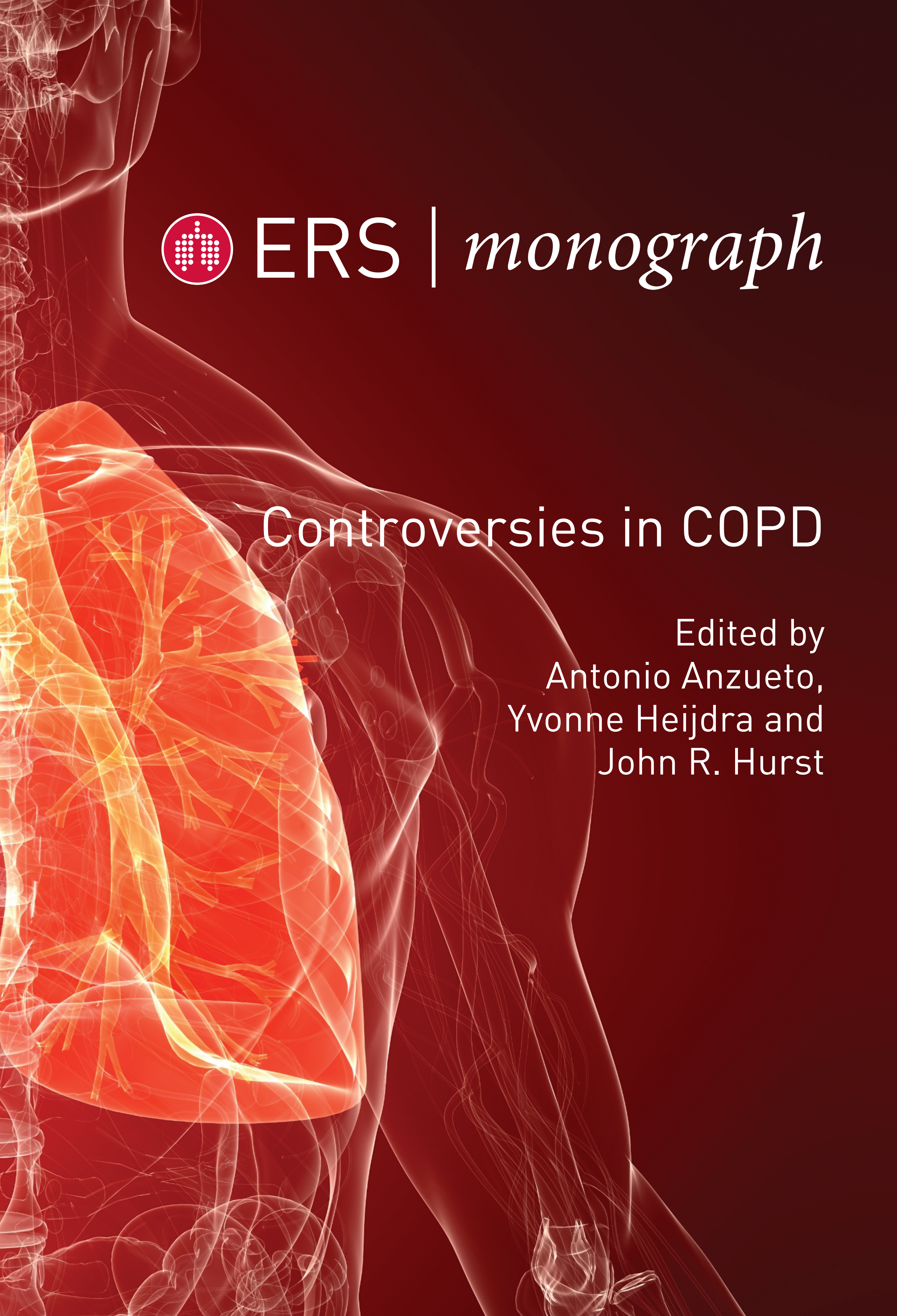

ERS | *monograph*

Controversies in COPD

Edited by
Antonio Anzueto,
Yvonne Heijdra and
John R. Hurst

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Antonio Anzueto, Yvonne Heijdra
and John R. Hurst

Editors in Chief
Tobias Welte (outgoing Editor)
Robert Bals (incoming Editor)

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Preface

Tobias Welte (outgoing Editor in Chief) and
Robert Bals (incoming Editor in Chief)

Tobias Welte

Robert Bals

After arteriosclerosis and stroke, COPD is one of the most common diseases worldwide. The morbidity, mortality and healthcare costs of COPD are high and will continue to rise due to the demographic changes expected. Since the beginning of the millennium, COPD has become one of the major areas of research. The improvement in quality of life, and perhaps in life expectancy, achieved since then is primarily due to the establishment of non-pharmacological measures, such as standardised smoking-cessation programmes, structured exercise therapy, and infection prevention with influenza and pneumococcal vaccination.

Progress in pharmacological therapy, however, has been low. The essential treatment components, such as β-mimetics, anticholinergics or ICSs, have been available for more than 50 years, and have improved in terms of duration of action, efficacy and mode of administration. However, more than 15 substances with new and different modes of action tested in clinical trials have failed to demonstrate activity and have not been approved for regular treatment. The dynamic development of new therapies for asthma may explain why most of the COPD substances failed. Better phenotyping of asthma patients made targeted pathophysiology-oriented treatment possible. COPD is a heterogeneous disease, and it is indisputable that there are different phenotypes; however, with the exception of α_1-ATD, these have not been well characterised in the past. Better characterisation of COPD patients using new biomarkers, advanced imaging properties and the whole spectrum of omics technology may stimulate the development of a new generation of drugs.

This issue of the *ERS Monograph* provides a comprehensive overview of the debate in this context, with consideration of the future direction of COPD research and clinical practice. We would like to thank the Guest Editors Antonio Anzueto, Yvonne Heijdra and John R. Hurst for their excellent work in bringing together this interesting and wide-ranging selection of chapters. We hope that both clinicians and scientists will find this book

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useful, and that it will stimulate further discussion about the diverse and fascinating disease, COPD.

With this issue Tobias Welte says goodbye after 5 years as Editor in Chief of the *ERS Monograph*. It has been a wonderful time, during which the *Monograph* has continuously developed. I have learned a lot, gained a lot of friends and have always appreciated working with the ERS Publications Office. Many thanks to all who have supported me in the past.

Robert Bals will take over the role of Editor in Chief from now on. Knowing him very well, I am convinced that he will be successful in improving the *ERS Monograph* further. Good luck Robert.

Guest Editors

Antonio Anzueto

Antonio Anzueto is currently Professor of Medicine at the University of Texas Health Sciences Center at San Antonio, TX, USA, and the Chief of the Pulmonary Disease Section at The South Texan Veterans Health Care System. He is a faculty member in the Pulmonary Disease and Critical Care Medicine division. He earned his Doctor of Medicine degree at the Universidad de San Carlos de Guatemala, Guatemala City, Guatemala, and completed his training at both Hospital General San Juan de Dios, Guatemala City, and the University of Texas Health Science Center.

Antonio Anzueto is a reviewer for most prestigious scientific journals, including *The New England Journal of Medicine*, *JAMA*, the *European Respiratory Journal* and the *American Journal of Respiratory and Critical Care Medicine*. He is a member of the scientific committee of the Global Initiative for Chronic Obstructive Lung Disease, the 2011 American–European Consensus Conference on ARDS, the European Respiratory Society/American Thoracic Society Acute Exacerbations Task Force, and many other medical institutional and organisational committees.

Antonio Anzueto has published over to 250 papers in peer-review journals, such as *The New England Journal of Medicine*, *JAMA*, the *European Respiratory Journal*, the *American Journal of Respiratory and Critical Care Medicine*, *Intensive Care Medicine*, the *Lancet* and the *Archives of Internal Medicine*, and has vast experience as an invited speaker and moderator at many scientific meetings. His areas of interest include COPD, pulmonary infections including chronic bronchitis and community-acquired pneumonia, sepsis, and acute respiratory distress syndrome. He is the recipient of a number of awards ranging from the Du Pont/American College of Chest Physicians Young Investigator Award to the Outstanding Teacher Award from the University of Texas Health Science Center.

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Yvonne Heijdra

Yvonne Heijdra studied medicine at the Radboud University Medical Centre (RUMC), Nijmegen, the Netherlands, where she obtained her medical degree. Thereafter, she specialised in internal medicine, followed by pulmonary medicine, combined with a PhD research project on respiratory muscle function and nocturnal oxygenation in COPD patients. She obtained her PhD in 1995 and registered as a pulmonologist in 1997. She became a staff member at the pulmonary department of the RUMC. In addition to her clinical activities, she was head of the pulmonary function department. In 2000, she worked for 1 year at Saint Elisabeth Medical Centre, a Tufts University-affiliated hospital, in Boston, MA, USA, to perform COPD-related research in the field of dynamic hyperinflation with Prof. Bartolome Celli. In 2006, she became an associate professor at the RUMC. Her fields of professional interest include COPD, pulmonary hypertension and clinical physiology. She leads the research performed in the field of COPD, especially related to (dynamic) hyperinflation. Her research aims to improve physical activity in COPD patients, which may result in an increased health status. She has published over 100 peer-reviewed papers. She was scientific secretary of the board of the Netherlands Society of Physicians in Pulmonary Medicine and Tuberculosis (NVALT) in 2011. In 2013, she was made president of the NVALT, and since 2015, she has served as vice president of the NVALT.

John R. Hurst

John R. Hurst graduated from the University of Edinburgh Medical School, Edinburgh, UK, in 1997 and was appointed Senior Lecturer, then Reader in Respiratory Medicine at University College London, London, UK, in October 2007. He has a research interest in the mechanisms of exacerbation susceptibility and cardiovascular risk as applied to COPD and bronchiectasis. This extends to α_1-ATD, lung disease in primary immunodeficiency and the adult consequences of prematurity. He was awarded the 2012 European Respiratory Society COPD research prize. His h-index is 21 with 76 citations listed on PubMed. His clinical work at Royal Free London NHS Foundation Trust focuses on the Specialist COPD and Bronchiectasis services, and he has an active role in undergraduate and postgraduate medical education. A previous Associate Editor at *Thorax*, he was appointed to the Editorial Board of the *American Journal of Respiratory and Critical Care Medicine* in 2012.

Introduction

Antonio Anzueto[1], Yvonne Heijdra[2] and John R. Hurst[3]

COPD is common but that does not mean it is easy to understand and manage. Our patients deserve excellent care, wherever they live. We define excellent as world-class, patient-centred, evidence-based and cost-effective multidisciplinary care from diagnosis to death.

The complexity of COPD is now more widely recognised, and with that comes care directed towards each patient's specific demographic and clinical characteristics (phenotype) or, more likely, phenotypes. We all face, in our everyday practice, areas of controversy in COPD. Evidence-based medicine is often not available. For example, how would you alter the management for a COPD patient with α_1-ATD? Can COPD arise as a consequence of premature birth? How should ACOS and COPD–bronchiectasis overlap syndrome be managed? What is the value of CT in COPD? Is there a difference between a COPD exacerbation and pneumonia?

It is timely, then, to consider where the current controversies in COPD may lie. Developed from an idea discussed at the European Respiratory Society International Congress in 2014, we are delighted to present this *ERS Monograph* at the 2015 Congress. Our international expert authors have produced a monograph that addresses the key current controversies in a way that we hope is both relevant to the clinician through the use of case vignettes, whilst illustrated by state-of-the-art science and clinical evidence.

We hope you enjoy reading this *Monograph* recognising the described controversies and that you take these concepts back to the clinic to improve the care of patients with COPD. Fundamentally, that is why we all do what we do.

We would like to take this opportunity to thank all the authors, reviewers and ERS Publications staff for their commitment and enthusiasm for the project.

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List of abbreviations

6MWD	6-min walk distance
6MWT	6-min walk test
α_1-AT	α_1-antitrypsin
α_1-ATD	α_1-antitrypsin deficiency
ACOS	Asthma–COPD overlap syndrome
AECOPD	Acute exacerbations of COPD
AHR	Airway hyperresponsiveness
BMI	Body mass index
BODE	BMI, airflow obstruction, dyspnoea, exercise capacity
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computed tomography
D_{LCO}	Diffusing capacity of the lung for carbon monoxide
FEF$_{25–75\%}$	Forced expiratory flow at 25–75% of FVC
F_{eNO}	Exhaled nitric oxide fraction
FEV$_1$	Forced expiratory volume in 1 s
FFM	Fat-free mass
FVC	Forced vital capacity
HRCT	High-resolution computed tomography
ICS	Inhaled corticosteroid
IL	Interleukin
ILD	Interstitial lung disease
K_{CO}	Transfer coefficient of the lung for carbon monoxide
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PR	Pulmonary rehabilitation
PPM	Potentially pathogenic microorganism
QALYs	Quality-adjusted life-years
TNF	Tumour necrosis factor

Screening and case finding

Joan B. Soriano[1] and David Price[2,3,4]

Case history: A 60-year-old male presents to his general practitioner with grade 2 dyspnoea on the modified Medical Research Council (MRC) Dyspnoea Scale. In the previous week, at his yearly occupational (a large car repair workshop) check-up, his peak flow was measured and simple spirometry was performed. The occupational nurse identified potential airflow limitation. He is atopic and was a smoker up to 10 years ago, totalling a 20 pack-year smoking history. He was/is very physically active: he walks 2 km to work every work day and still plays football once a week, although he states that since last winter he has had to play in goal for the second half. He has never received any respiratory medication. What are the next steps?

Chapter summary: Our knowledge of COPD has widely expanded after decades of intensive clinical research. However, there remain many controversies surrounding when, where, by whom and for whom COPD screening and case finding with spirometry and other tools should be conducted, and often recommendations are not evidence based. Is a case like that described above worth further exploration? If it is confirmed, why was a signal of airflow limitation not picked up in previous annual check-ups (figure 1)? When does such an active worker (and sportsman) become a patient? And would you rule out asthma or ACOS? Meanwhile, COPD remains significantly underdiagnosed, with diagnosis commonly missed or delayed until the condition is advanced. It is envisaged that early diagnosis of COPD should have an impact on individual and population outcomes, but definitive confirmation proves elusive. Despite significant effort and investment, the implementation of quality spirometry is limited because of a number of hurdles and limitations, some of which are described in this chapter. The routine use of spirometry in primary care in all patients with respiratory symptoms should reduce COPD underdiagnosis.

COPD is a disorder that causes significant morbidity and mortality globally. According to the latest World Health Organization (WHO) update, it causes the death of ⩾2.9 million people annually and in 2013, was the 12th cause of global years of life lost [1]. It is still projected to be the third leading cause of death by 2020 [2, 3]. Subsequent to that date, even assuming the most pessimistic scenario regarding the global spread of HIV/AIDS, by 2030 COPD will be the direct underlying cause of 7.8% of all deaths and will represent 27% of deaths related to smoking, only surpassed by 33% for cancer and 29% for cardiovascular disease [4]. COPD may also be a significant, independent risk factor for deaths from other causes, such as heart disease and lung cancer, and its treatment and

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	Ref.	Obs.	%	Post-BD L	Post-BD %
FVC L	4.76	4.34	91	4.73	+8
FEV_1 L	3.28	1.77	54	2.12	+18
FEV_1/FVC %	70	41		45	
$FEF_{25-75\%}$ $L \cdot s^{-1}$	2.30	0.44	19	0.66	+40
PEF $L \cdot s^{-1}$	9.26	4.96	54	5.45	+9

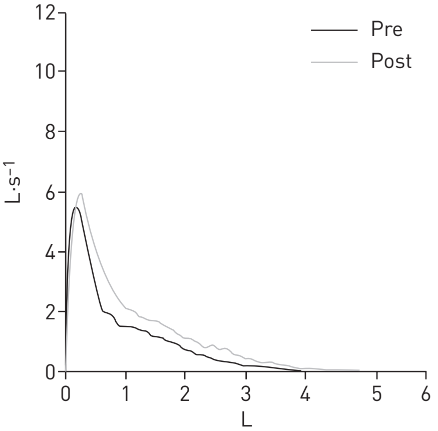


Figure 1. Spirometry of the patient in the Case history. Ref.: reference; Obs.: observation; BD: bronchodilator; PEF: peak expiratory flow.

consequences may worsen other diseases like diabetes [5, 6]. Besides being a cause of death, the prevalence and consequent burden of COPD is also expected to increase with rapidly rising smoking rates in developing countries, more than making up for the small reductions in more developed countries. This, combined with an ageing population with ageing lungs, is responsible for the actual and forecasted rapid increase in COPD.

At 1.1 billion, there have never be so many smokers in the world as there are now; similarly, at 328 million, there have never been so many people with COPD [7]. Results from the landmark Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO) [8] and the Burden of Obstructive Lung Disease (BOLD) [9] initiatives indicate a higher and more variable prevalence of COPD than previously anticipated. Overall, the prevalence of COPD in the general population is estimated to be ~1% across all ages, rising steeply to 8–10% or higher amongst those aged ⩾40 years [10].

Consistently, all population studies in which post-bronchodilator spirometry was conducted and which had available information on previous COPD-compatible diagnosis/underdiagnosis (Estudio Epidemiológico de la EPOC en España (IBERPOC) [11], PLATINO [5], the study by Bednarek *et al.* [12], and Obstructive Lung Disease in Northern Sweden (OLIN) [13]) have found that underdiagnosis of COPD is high, averaging ⩽80% in most areas reported, independent of overall prevalence [14]. The lowest rate of underdiagnosis of COPD was 72.0% in Madrid, Spain (IBERPOC), whilst the highest was 92.5% in Montevideo, Uruguay (PLATINO). But misdiagnosis is also common [15]. These estimates of COPD underdiagnosis are substantially higher than those reported for high blood pressure, hypercholesterolaemia and other similar conditions.

Within Europe, recorded prevalence, hospital admissions and deaths are only the "tip of the iceberg" [16]. From the total 505 million people in the 28 European Union (EU) member states, and only considering the 260 million who are ⩾40 years of age, it has been estimated that 23 million have COPD of moderate or higher severity, and 17 million have stage I COPD [16]. With a minimum COPD underdiagnosis rate of 70%, it can be extrapolated that 28 million Europeans are not yet diagnosed and therefore remain untreated. These estimates of COPD underdiagnosis are substantially higher than those reported for high blood pressure, hypercholesterolaemia and other similar conditions.

At the individual level, undiagnosed airflow obstruction has a dose–response gradient for several unspecific adverse health effects like poor general health status, difficulty when walking or carrying weights, and even needing help with personal care [17]. With increasing retirement ages, COPD symptoms often occur at a working age and, if not diagnosed and treated, may result in early retirement with a consequent impact on personal and societal economic burden. In the very elderly, there are limitations to quantifying COPD burden. Recent advances in reference equations, now valid in those ⩽95 years of age, may facilitate quantification and reduce the magnitude of its related burden [18]. Regrettably, previous attempts to determine the specific reasons for COPD underdiagnosis at the population level, and to relate it to smoking patterns, ageing, poverty, sedentarism, COPD mortality rates or other related indicators, at the international or national level, have been unsuccessful. A recent paper examining UK primary care over a 20-year period showed many missed opportunities, both in primary and secondary care, where COPD should have been considered. These opportunities included consultations for lower respiratory tract infections, provision of chest radiographs for respiratory symptoms and even hospitalisation with respiratory tract infections [19]. Accurate diagnosis of COPD is important in order to initiate timely risk factor modification and therapy, and to avoid unnecessary costs and potential side-effects in those unlikely to benefit from therapy. The former implies offering smoking cessation according to locally available resources, while the latter requires hygiene interventions, vaccinations, avoidance of sedentary living and individualisation of management within the current wealth of treatment options. Most important to the reduction of underdiagnosis is the routine use of spirometry in primary care in all patients with respiratory symptoms either case exclusion using microspirometry or ideally full spirometry.

Prevention

There is potential for the prevention of COPD at all levels, primary to tertiary (figure 2). Primary prevention could be achieved by modifying or reducing its main causal risk factor, cigarette smoking, or other known risk factors [16]. Secondary prevention would target screening or early detection of COPD, often by means of spirometry, individual symptoms or a combination of both. Finally, tertiary prevention of COPD is meant for the management of identified COPD individuals to improve health status, minimise activity limitation, reduce or slow progression, and reduce exacerbations and other adverse outcomes. Certainly, the airflow limitation of some initially diagnosed COPD patients might improve or even "reverse" to normal, spontaneously or after treatment, so differential diagnosis should be reviewed, eventually with new tests.

However, some consider that regular monitoring of lung function in the follow-up of patients with COPD has not been shown to influence their health status [20], stating that applying the same, fixed frequency for monitoring lung function in all patients diagnosed with COPD is probably rather inefficient, which is something that most guidelines do not yet recognise. However, as discussed later, it is our belief that spirometry has a role at all three levels of COPD prevention.

Early diagnosis of COPD may be compared to screening programmes for hypertension and hyperlipidaemia. Both diseases have a very long, asymptomatic course before life-endangering symptoms or signs of vascular disease appear. Programmes targeted at reducing hypertension and hyperlipidaemia have greatly reduced deaths from acute myocardial infarction or stroke in

Level of prevention	**Primary: risk factor reduction**		**Secondary: screening**				**Tertiary management of existing disease**		
Aim	Prevent smoking and other risk factors.	Reduce smoking and other risk factors pre-COPD identification.	Early detection of asymptomatic COPD.	Early detection of symptomatic COPD.			Correcting misdiagnosis (otherwise beyond scope of this review).		
Population to target	Whole population.	Smokers	Smokers without symptoms.	Case-finding approaches to populations or those consulting who are "at risk".			Those diagnosed as asthma or other chronic respiratory disease (bronchiectasis,tuberculosis) >40 years of age *etc.*		
Identification method	Pre-BD spirometry.		Pre-BD spirometry.	Questionnaires followed by diagnostic post-BD standard spirometry.	Spirometry to exclude COPD followed by diagnostic post-BD standard spirometry.	Diagnostic post-BD standard spirometry.	Questionnaires, followed by diagnostic post-BD standard spirometry.	Spirometry to exclude COPD, followed by diagnostic post-BD standard spirometry.	Diagnostic post-BD standard spirometry.
Examples in other diseases	Promoting healthy habits for hypertension or hyperlipidaemia.	Reduce smoking and other risk factors.	Fasting glucose test to screen for diabetes.	Fasting glucose or glucose tolerance for screening of diabetes.			Monitoring and risk management of cardiovascular or diabetic consequences.		
Potential benefits	Smoking prevention to reduce risk of developing COPD and other comorbidities.		By early screening, prevent or delay progression to symptomatic COPD through smoking cessation.	Smoking cessation and other interventions to reduce progression. Improve current health status and reduce impact of disease through proven healthcare interventions. Reduce risk of events such as exacerbations and potentially deaths through proven healthcare interventions. Identify other lung diseases *e.g.* restrictive lung disease if spirometry performed.			Reduce inappropriate treatment and associated risks. Smoking cessation and other interventions to reduce progression. Improve current health status and reduce impact of disease through proven healthcare interventions. Reduce risk of events such as exacerbations and potentially deaths through proven healthcare interventions. Identify other lung diseases *e.g.* restrictive lung disease if spirometry performed.		
Potential harm	None		May encourage "healthy smokers" to continue smoking. May medicalise normal variation, especially in the elderly.	May encourage "healthy smokers" to continue smoking. Questionnaires and spirometry to exclude COPD may miss early disease and may delay clinical presentation. Will miss those with asymptomatic disease.			Differential diagnosis not always clear-cut and may lead to confusion in clinical practice. There is little guidance on how to treat those patients with mixed disease.		
Potential setting	Community		Community	Community Primary care Pharmacy and other			Primary and secondary care.		
Workload implications	Substantial *via* lobbying and political/media pressure.		Studies suggest need to undertake diagnostic spirometry on five people to find one patient with COPD, but depends on baseline risk. Those based on questionnaires suggest 1:2 to 1:3 who are "positive" have COPD.	If symptoms are required to undertake any of the screening methods, the numbers needed to screen are likely to be smaller than for the early detection of asymptomatic disease. Substantial resources and training required.			Likely to be relatively small beyond those already in practice.		
Research required	Available	Benefit unknown.	Benefits mixed in studies to date. Inconclusive or negative studies have been considered to shadow others.				No studies of benefit/harm of this approach have been undertaken.		

Figure 2. Screening spirometry: practical implications, feasibility and impact. BD: bronchodilator.

the USA [21–23]. To date, such evidence is absent on general population improvements in lung function, reductions in COPD exacerbations, or other COPD outcomes and end-points [24]. This may simply be because the appropriate studies have not yet been conducted.

Fortunately, many national and international guidelines offer some consensus on the definition and staging of COPD. Yet it appears there is no consensus on how, when and where spirometry and other tools should be used to screen for COPD, if at all.

Spirometry

Spirometry is the most robust of the commonly used pulmonary function tests, although it is not the easiest to conduct. It measures lung function, specifically the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled. Spirometry can have many different uses, and it enables any appropriately trained healthcare professional with access to the right equipment or a spirometry service to make an objective measurement of airflow obstruction and the degree to which it is reversible. It is an important tool for the accurate diagnosis and effective management of chronic respiratory diseases, including asthma and COPD. Clinicians at the primary [25] and specialised respiratory [26] level consistently agree that good-quality spirometry should be implemented more extensively if we are to achieve a real public health impact to reduce the COPD burden. Spirometry, as a diagnostic test, fulfils the criteria of being a reliable, simple, noninvasive, safe and nonexpensive procedure to detect airflow obstruction. Spirometry is recognised by international clinical guidelines as the essential test for making a COPD diagnosis [27]. So-called case-finding spirometry is also recommended by a number of bodies, as a tool in community settings, either used in conjunction with questionnaires or on its own to rule out COPD [28].

Spirometry in clinical guidelines

A small but significant step forward was the agreement on spirometry thresholds for diagnosis and severity by the American Thoracic Society (ATS)/European Respiratory Society (ERS) COPD guidelines [27], the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [29, 30], UK NICE [31] and the Spanish COPD Guidelines (GesEPOC) [32]. An FEV_1/FVC ratio of <0.70 when measured after administration of an inhaled bronchodilator is the spirometric criterion to define COPD. However, the ATS/ERS guidelines on standards for the diagnosis and management of patients with COPD recommend the use of the lower limit of normal or the FEV_1/FVC, as the use of a fixed ratio FEV_1/FVC may decrease with increasing age, leading to the potential for overestimation of airflow obstruction in older individuals and underestimation of airflow obstruction in the young ones; the incremental benefits of any changes from current thresholds remain to be seen [33, 34].

"Case finding" *versus* "population screening"

More than 25 years ago, Geoffrey Rose lectured on a general, theoretical model of disease [35]. Counter-intuitively, he postulated that for any disease caused by a necessary agent within a population, the determinants of this disease in individual cases, and the determinants of the incidence rate in the population, might differ. The corresponding strategies in control are the "high-risk" approach, which seeks to protect susceptible individuals, and the population approach, which seeks to control the causes of incidence.

The two approaches are not usually in competition, but the primary concern should always be to discover and control the causes of incidence. Perhaps there is no better example of this dualism than COPD.

As discussed earlier, COPD is a very common disease that is often undiagnosed or misdiagnosed. Recent estimates put the percentage of those >40 years of age who smoke and do not have a diagnosis of COPD but actually have COPD at approximately one in five [17], and the proportion of those >40 years of age who are diagnosed as having asthma but actually have COPD at about one in three [36].

A recent American College of Physicians statement paper categorically concludes: "In patients with respiratory symptoms, particularly dyspnea, spirometry should be performed to diagnose airflow obstruction. Spirometry should not be used to screen for airflow obstruction in asymptomatic individuals. (Grade: strong recommendation, moderate-quality evidence.)" [37]. Several issues relate to earlier diagnosis in terms of costs and benefits of identification of groups with increasing risk and severity. For the sake of simplicity, they are hereafter presented as: at-risk of COPD; those with a pre-COPD condition; and those with established and then clinical COPD with increasingly recognisable severity (GOLD stages I to IV). All but the last would require some form of screening, whilst the latter could also be undertaken using case identification in clinical practice, so called "case finding".

Identification of people at increased risk of developing COPD

Other risk factors for developing COPD, beyond tobacco smoking, are being increasingly recognised [15], and include many other environmental exposures like occupational exposures to dust and fumes in developed and developing countries [38], and indoor biomass fuel burning in many developing countries [39]. Reduction of such exposures on a population basis or at an individual level might be worthwhile. Factors that seem to be less important in the development of COPD, although they may worsen disease, include outdoor pollutants and passive smoke exposure. It may not currently be possible to modify a number of factors associated with COPD development; these include the ageing lung, sex, comorbidities and repeated respiratory infections in children or adults. The best known genetic factor linked with COPD is α_1-ATD, which arises in up to 3% of patients with COPD and combined with smoking, increases the risk of panlobular emphysema [40]. Several other genes have been implicated in COPD but the consistency of their effect in the development of COPD is currently unproven. The one comorbid disease consistently shown to be associated with COPD development is asthma, and it appears that people with asthma who smoke lose lung function more rapidly than individuals without asthma [41]. At this early stage, spirometry as a screening tool for disease has only been explored in α_1-ATD probands and their relatives, smokers and those with occupational exposures; apart from marihuana users [42, 43] and those with biomass exposure in selected developing countries [44], it is unlikely screening will prove successful with other types of exposures.

In terms of a definite pre-clinical phase with no observable lung obstruction by current standards, it is now recognised that the initial stage of the disease is damage to lung tissue, including emphysema and airway inflammation [45]. Although this may cause some degree of narrowing of the airways, a small degree of airway narrowing may be undetectable for many years, even if sequentially tested with spirometry [46]. Early disease at this stage may be truly asymptomatic. However, it is plausible that even seemingly asymptomatic individuals with disease are affected in ways that are difficult to perceive, such as impaired strenuous physical exertion.

People in the initial stages of developing COPD may also be overtly symptomatic, but still show no signs of airway obstruction [47]. This was formerly referred to as GOLD stage 0, which was defined as "at risk" of developing definitive COPD. Currently, GOLD stage 0 has been removed from the guidelines, due to insufficient evidence that all people in this group necessarily develop COPD [48]. It should be remembered, however, that some people in this group do have the early pathological changes of COPD that cannot be confirmed using spirometry [49]. Their symptoms may include a persistent cough that is associated with an increased risk of future COPD development, excessive sputum production or recurring chest infections, none of which are specific to COPD, which adds to the challenge of making a correct diagnosis. They may also suffer from repeated respiratory tract infection, which may further accelerate lung function decline.

A US Preventive Services Task Force panel concluded that adults would not be screened for COPD using spirometry, as no evidence is available for the later prevention of COPD exacerbations or for improvements in respiratory-related health status [50]. It is likely we will never have such evidence. Because of the lack of proven progression, the approach at this stage might be interventions to reduce the likelihood of developing future COPD, as one might manage high cholesterol or raised blood pressure. Techniques for screening may include determining "lung age" with spirometry (figure 3), questionnaires and other respiratory assessments, as discussed later.

Pre-clinical COPD

A programme for an active search for COPD in its pre-clinical stage, that is performed before fulfilling current COPD spirometric thresholds to define COPD, would require the allocation of funding. Certain criteria should be accomplished before undertaking large-scale actions to detect a specific disease in its pre-clinical stage. In a similar manner to a vaccination programme, as far as early diagnosis of COPD is concerned, three

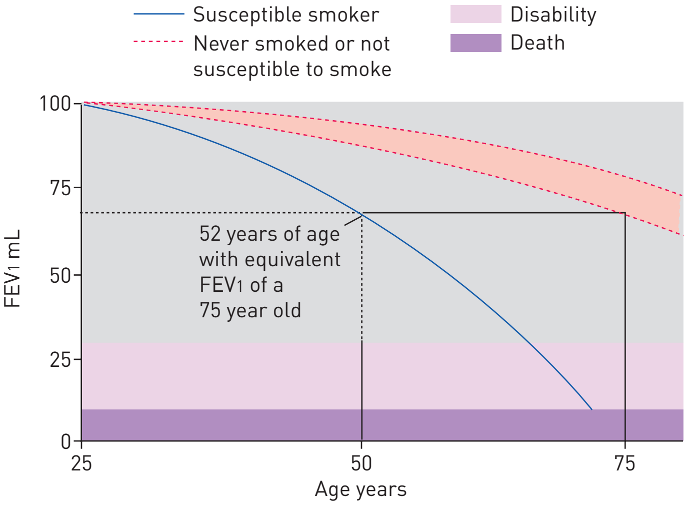


Figure 3. Lung age estimation. Reproduced and modified from [51] with permission from the publisher.

principal criteria should be considered: 1) undetected disease would go on to cause substantial morbidity and mortality; 2) treatment of risk factors has a major impact upon the subsequent development of disease; and 3) an objective test that is relatively simple, affordable and safe is available to confirm the disease. COPD fulfils all these criteria. As discussed at the beginning of this chapter, 3 million people die each year from COPD worldwide, with tobacco smoke being by far the most common risk factor, responsible for >80% of all cases [52]. If smoking behaviour is amenable to change, and we accept that accelerated FEV1 decline is a marker of COPD development, there are beneficial effects of smoking cessation.

Peto *et al.* [53] were the first to prospectively investigate the effects of smoking cessation on accelerated lung function loss in 2718 males with smoking-related disease. Patients with an FEV1 <70% predicted at 25 years of age, and accelerated loss of ventilatory reserves, who stopped smoking at 45 years of age, changed their slope of FEV1 decline to that observed in healthy nonsmokers. Patients who stopped smoking at 65 years of age, and whose FEV1 at that time was reduced to 30% pred, showed improved survival compared with patients who continued to smoke.

Established COPD

Perhaps the most elegant, influential, prospective spirometry data in COPD patients were collected in the Lung Health Study (LHS) [54]. Around 6000 subjects with mild-to-moderate COPD (mean FEV1 78% pred) were studied from >70 000 current smokers of 35–59 years of age; subjects were recruited using advertisements and were offered a smoking-cessation programme. Around 25% of the total completely stopped smoking and 22% remained nonsmokers to the end of study. Both groups were followed up for 5 years with spirometric tests performed every 12 months. Subjects who stopped smoking showed a small improvement in lung function over the first year, a mean rise in FEV1 of 57 mL, and had reduced rates of decline for the remaining 4 years of the study (mean 34 mL·year^{-1}). Subtle improvements (or worsening) associated with quitting or resuming smoking were observed even after 1 year within each LHS follow-up visit [55]. Those who continued to smoke lost 63 mL of their FEV1 per year. Another significant finding in this relatively young cohort came from studying the 149 deaths during the 5 years of follow-up. The majority of deaths were caused by smoking-related diseases: lung cancer and coronary artery disease. 11 years after LHS entry, 77% of surviving participants were evaluated again [56]. 93% of participants who were nonsmokers for the 5 years were still abstinent at 11 years. Differences in lung function decline between smokers and nonsmokers persisted, averaging 30 mL per year in nonsmokers and 60 mL per year in continuing smokers. Only a few patients progressed to severe COPD. Further follow-up showed that intermittent smokers also benefited from less accelerated lung function decline [57]. A separate analysis of the effects of quitting on reducing symptoms was performed. The results concluded swift and sustained reductions in symptoms of cough, phlegm and wheeze in smokers who were able to quit. >80% of sustained quitters who had chronic cough at baseline when still smoking reported that they no longer had cough 1 year later [58].

Most population studies indicate that with spirometry conducted at this stage, 30–50% or more of COPD cases identified early will be of mild severity [12]. It is useful to have them diagnosed and followed, to further document the natural course of the disease [59–61].

We agree with the SAPALDIA (Swiss study on Air Pollution and Lung Disease in adults) investigators that in population-based studies, as well as in any individual patient assessment, respiratory symptoms are of major importance for predicting long-term clinical outcomes in subjects with COPD with mild obstruction. Population studies based on spirometry only may misestimate the prevalence of clinically relevant COPD [12].

Clinical COPD

Identifying patients with symptomatic and clinically active COPD remains a significant challenge. Many patients will have consulted and either the diagnosis has not been considered, it has been labelled as "smokers' cough", or it has been suggested to be another condition, such as repeated lower respiratory tract infection or asthma. For those who have not consulted, this may be because they are in denial of their condition, see it as a health problem not an illness, or because have a negative impression of the value of consulting [62].

This stage is probably the least contentious area in identifying COPD and can either be done by screening populations or case finding within clinical settings. Instruments that can be applied include: questionnaires to reduce the number needing spirometry to find a case; screening standard spirometry (*i.e.* spirometry of a sufficient standard to rule out COPD); and full standard spirometry [63].

van Schayck *et al.* [64] were probably the first to apply the case-finding approach to early diagnosis of COPD, although their approach was only to target active smokers. Active smokers aged 35–70 years visiting two primary care offices were asked to perform spirometry tests. 85% of 201 smokers not taking drugs for pulmonary conditions performed reliable spirometry. 18% of them presented with an FEV_1 <80% pred, 9.5% in a group of 35–40 year olds and 21% in a group of ⩾40 year olds. The authors concluded that testing one smoker a day, an average practice, could identify one patient with COPD a week. The crucial role of spirometry in the early diagnosis of COPD was confirmed by Buffels *et al.* [65] who prospectively surveyed the population of those aged 35–70 years visiting 22 general practitioners during a 12-week period. Spirometry was performed in all subjects with respiratory symptoms and in a 10% random sample without respiratory complaints (n=3408). Spirometry confirmed airflow obstruction in 17.8% of subjects with respiratory symptoms and in 4% of subjects without respiratory symptoms. As the group without complaints was much larger (77% of the total), spirometry increased the total number of detected subjects with airflow obstruction by 42%. Several questionnaires have now been developed that appear to reduce the number of smokers needing spirometry to identify COPD by at least a factor of two, and may be further refined by combining with the use of case-finding spirometry [66].

Epidemiological surveys aimed at screening for airflow obstruction also identify a substantial number of individuals with a restrictive pattern, up to 6.6% of adults in the third National Health and Nutrition Examination Survey (NHANES III) [67]. Although it is unlikely that this reflects pulmonary fibrosis or other clinical syndromes with a bad prognosis, and they are likely to be associated with less technically valid manoeuvres, a restrictive pattern is associated with both unspecific and respiratory burden [68, 69]; further research is currently under way.

Controversial issues

There has been a historical nihilism surrounding COPD, with patients, and even their doctors, establishing blame and blatantly denying the elephant in the room. The recommendations on what individuals to screen for COPD, and when and how, differ at the primary and specialised care level [13, 24]. The recent availability of new treatments and strategies to offer to COPD patients is opening new perspectives, but more contentious issues remain (figure 2).

Pre- *versus* post-bronchodilator values for screening

All international COPD guidelines insist on post-bronchodilator values. FEV_1 and other respiratory indices without bronchodilation are fine markers of overall health. The usefulness of the simplest spirometry pre-bronchodilator manoeuvre, vital capacity, to predict long-term total and cardiovascular mortality even better than cholesterol, blood pressure or other biomarkers, has long been established [70].

Interestingly, authors and guideline recommendations differ on how and when to conduct bronchodilation. Single or combined drugs with a range in dosing (40–80 mcg of ipratropium and/or 100, 200 or 400 mcg salbutamol), with timing of manoeuvres repeated from baseline 10 to 30 min (or other) after inhalation. The suggested threshold to define a positive bronchodilation test (an increase in FEV_1 of more than 12% and 200 mL from the pre-bronchodilator value) in asthma [71], is variably accepted in COPD guidelines, with many suggesting minimal limits of 300 or 400 mL. Of course, all results will depend on the choice of reference equations, grossly unavailable for most populations. Provocatively, if the bronchodilatation method is not standardised as previously discussed, why do guidelines call for post-bronchodilator values to assess COPD severity and for irreversibility, if treatments appear to work equally well across all levels of reversibility [72]? From a public health point of view, a related, relevant issue in respiratory medicine is perhaps that current views of “reversibility” misclassify large segments of the population [73], resulting in a significant portion of asthmatic sufferers (smokers and the elderly) and COPD sufferers (the ones with a positive bronchodilator test) being excluded from clinical trials. Therefore, their respective treatment is not evidence based.

Local reference values

Globally, the European Coal and Steel Community (ECSC), Hankinson’s reference equations derived from NHANES III [74] and, more recently, Philip Quanjer’s Global Lung Function Initiative (GLI) equations [18], are widely used to calculate reference values according to age, sex, height and ethnic origin. However, for most populations worldwide, the unavailability of local reference values for estimating predicted values [6, 7], and the largely unknown natural history of lung function and COPD, remain as hurdles for the accurate interpretation of any individual spirometry. It is commendable that a new initiative aiming to collect spirometry data from different studies and centres, proposes a new way of collating and analysing spirometric data from population surveys. It is aimed at developing reference ranges that more accurately describe the non-linear relationship between spirometric lung function and height by: age; an extension of the LMS (lambda, mu, sigma) method [75], the same statistically advanced method that is used to generate growth curves for children; other methods. Elsewhere, there are elegant discussions on the advantages and limitations of using reference equations that use height, age or other parameters like z-scores, in schoolchildren and adolescents in particular [76], and we agree that limitations remain for describing the progression of pulmonary function and the natural course of respiratory disease.

Using all manoeuvres/reducing stringent quality control criteria

The goal of spirometry interpretation is to distinguish normal from abnormal. In contrast with other laboratory and clinical tests, spirometry results do require clinical interpretation, with a minimum time commitment of 2–10 min. Quality assessment is the first step, which takes place before further clinical interpretation of values and curves. The interpretation of a single value, like the FEV_1/FVC ratio, the lower limit of normal (another way of expressing the test results in relation to the distribution of this index in a healthy population) or other, should be assessed in conjunction with many others, as well as reviewing the shape of the best curves (*i.e.* flow/volume loops and timing) and several other quality control checkpoints, agreed in consensus by international experts [18]. Indeed, the selection of the manoeuvre/s, both pre- and post-bronchodilator, is quantifiable but is subject to observer arbitrary choice, and also by the arbitrary, albeit not necessarily irrational, choice of cut-off values, like FEV_1 % pred, and others [13, 77, 78].

The best clinical pulmonary function laboratories disregard ⩾20% of patient data, and this censored data can be >40% in population studies. However, emerging evidence suggests that previously quoted rates of technically inadequate tests seem to have been improved upon in recent studies, and collective efforts could reduce disregarded data. In a recent PLATINO report, factors significantly associated with failed spirometry, that is not able to produce acceptable manoeuvres were: ⩾70 years of age; a higher GOLD stage; female sex; and no education [79]. All these factors should be taken into account to quantify and tackle any future COPD epidemic. Away from clinical trials or in the specialised setting, the consideration of tests of a suboptimal quality might decrease the degree of uncertainty in clinical decision-making. For the diagnosis of a patient who conducted spirometry and performed forced blows with maximal effort many times, is it better to have some information than no information at all? The implications of the potential simplification of agreed data quality control remain to be investigated. Hand-held office spirometers have been developed in recent years, with a global quality and user-friendliness that makes them acceptable for use in general practices and population studies.

Screening as an aid to smoking cessation

It is well established that simple brief advice from a health professional increases the chances of smoking cessation [80]. Those with early lung damage are classically considered the group at risk of accelerated deterioration in lung function compared with nonsusceptible smokers or nonsmokers [81]. There is an urgent need to demonstrate the efficacy and effectiveness of any smoking intervention strategies. The difficulty in convincingly proving that biomedical risk assessments such as measurement of exhaled carbon monoxide, genetic susceptibility to lung cancer, or lung function-supported antismoking interventions work as we think they should, highlights the need for treating tobacco addiction as a chronic relapsing disorder. Any research on smoking cessation is extremely difficult to conduct and to get funded, and to date, pooled support of the notion that giving information about lung damage to smokers improves quit rates is inconclusive [16]; a significant effect has only been obtained in a single good-quality trial (figure 3) [51].

The primary care setting should be a fundamental hub for any antismoking intervention [80, 82, 83]. Efforts to establish primary care centres as hubs of spirometry for COPD screening and case finding, have been accompanied with mixed results and confusing recommendations not to conduct screening for early or asymptomatic COPD [84].

Spirometry in patient follow-up

After a medical diagnosis of COPD, it is recommended that patients conduct spirometry every 6 months or yearly. Right after diagnosis, this will confirm (or help to discard) the initial clinical impression, and should aid tailoring drug treatment and other interventions [14]. Collaterally, and apart from asthma, the finding of bronchiectasis or tuberculosis in individuals who smoke adds difficulty to the differential diagnosis of COPD, particularly in developing countries [85]. The epidemiological and clinical association of lung cancer with COPD is now considered incontrovertible. However, as "early" diagnosis of most lung cancers does not improve survival, the potential benefit of spirometry and COPD screening to detect lung cancer and improve outcome deserves further research.

A recently published general population survey of 1003 patients with COPD, most of them reporting moderate or severe dyspnoea and 41% with a prior hospitalisation for COPD, highlighted that only 10% of respondents knew their FEV1 compared with 79% who knew their blood pressure. On treatment, 72% reported taking medication for COPD, usually a short-acting bronchodilator, whereas 87% of patients with COPD and hypertension were taking an antihypertensive medication and 72% of patients with COPD and hypercholesterolaemia were taking a statin [86].

Innovation in questionnaires and technology

There is continuous progress with portable spirometers, and although difficulties with validation remain, some can display FEV1/FVC, the lower limit of normal or other indices, as well as flow/volume curves. Very recently, the use of peak flow to top up a screening symptoms questionnaire used to rule out severe COPD in population studies has been proposed [87]. As discussed, primary care remains the first gate for population screening, and quality control of spirometry is paramount. With spirometry, there is little possibility of harm, so the counter is time/money spent taken from a finite pool. Without hard evidence, it used to be said that poor quality spirometry was itself a bad sign for the patient. The great thing about spirometry is that virtually all technically bad results are in the direction of a low FVC, through early stops, and a low FEV1, through inadequate effort (but not necessarily a low FEV1/FVC ratio). Presumably, results that do not show normal values are checked and spirometry is repeated. A number of limitations remain to achieving highly acceptable and reproducible spirometry in primary care. Therefore, it has been suggested that "softening" the stringent ATS/ERS spirometry criteria [88] might make spirometry more accessible to primary care health professionals for the purpose of case exclusion at the point of consultation and to improve the rate of detection of COPD, with moderate success to date

Table 1. Summary of the International Primary Care Respiratory Group (IPCRG) recommendations and standards for spirometers used in primary care

Essential

- Measures mandatory parameters:
  - FEV_1
  - FEV_6 or FVC
  - Estimated FEV_1/FEV_6 or estimated FEV_1/FVC
  - Forced expiratory time
- Complies with minimum ATS/ERS technical criteria for acceptable tests and session repeatability
- Flow/volume loop and/or volume/time curve displayed during the manoeuvre
- Reliable and robust device (as demonstrated by *in vivo* studies)
- Easy to perform an accuracy check
- Simple cleaning and maintenance
- Report on reproducibility of manoeuvres provided
- Error report in clear and simple language, including suggestions to improve technique

Optimal (in addition to essential standards)

- Provides LLN for FEV_1, FVC, FEV_1/FEV_6, FEV_1/FVC as well as predicted mean values
- Software for estimation of FEV_1 reversibility
- PEF flow or forced expiratory time (as indicator of correct spirometry manoeuvre if no FVC or FEV_6 is available to calculate extrapolated volume)
- Links to other software including patient records
- Error messages appear automatically in the following situations (as a minimum):
  - Slow start – message (*e.g.* blow hard and fast right from the start) triggered when back extrapolation volume >150 mL or 5% (whichever is greater) and/or time to PEF >120 ms
  - Cough detected during the first second of the forced expiration manoeuvre
  - Premature stop – message (*e.g.* keep blowing out for longer) triggered when a rapid cessation of flow detected or no plateau or forced expiratory time <6 s (<3 s for children <1 year of age)

Ideal (in addition to optimal standards)

- Software for performing provocation test

ATS: American Thoracic Society; ERS: European Respiratory Society; LLN: lower limit of normal; PEF: peak expiratory flow. Reproduced and modified from [63] with permission from the publisher.

[89, 90]. Table 1 summarises the International Primary Care Respiratory Group (IPCRG) recommendations and standards for spirometers used in primary care.

Spirometry conducted away from the doctor's office: pharmacies, lung days in the community, *etc.*

The aims of spirometry performed at the primary care level might be to exclude those with normal lung function and identify those who require a more complete investigation for COPD. In this context, spirometry protocols and standards in primary care will differ from those of spirometry performed for the purpose of achieving a definitive diagnosis in specialised care. Pilot tests are being conducted to explore the use of non-medical venues to conduct spirometry. In particular, pharmacies might have some advantages, with recent reports suggesting that pharmacists were able to identify customers with respiratory symptoms and/or smokers in a population in which the majority were middle-aged subjects and had never been tested for COPD [91]. They conducted high-quality spirometry manoeuvres in 70% of subjects, finding one case of airflow obstruction for every five individuals tested, a rate that was similar to that reported in the primary care setting [57]. The same group replicated their findings in a much larger study [92]. If confirmed in other studies, pharmacies could be an additional, useful venue to screen COPD in individuals at risk. Even venues that are not health related, or special events like spirometry days or COPD days, provide the potential for public health interventions [93]; however, completely opposed opinions can be found elsewhere [94]. Screening at all levels can be undertaken in the community or in healthcare-based settings. Maintaining standards of quality of diagnostic spirometry is fundamental to the accurate diagnosis of COPD, and may be challenging in low-income countries. Here, the disadvantages of under- and overdiagnosis based on lower standard spirometry needs to be weighed against the disadvantages of both undertreatment of those not diagnosed with COPD or misdiagnosed as having other conditions, and overtreatment when chasing COPD symptoms, with the potential for harm in terms of the side-effects related to unnecessary treatment, and wasted healthcare resources.

To reduce underdiagnosis, the most important factor is the routine use of spirometry in primary care in all patients with respiratory symptoms. Further, two main strategies can be envisaged: mass screening with spirometry and case-finding strategies. Both have advantages and limitations, but in both, collaboration with primary care physicians and nurses is fundamental [95]. There are a number of initiatives exploring the use of unconventional settings (*e.g.* pharmacies) and the single or combined use of questionnaires (*e.g.* COPD Population Screener Questionnaire [96]), alongside other tools like peak flow with a threshold of 2.2 $\mathrm{L{\cdot}s^{-1}{\cdot}m^{-2}}$ pre-bronchodilator [97], COPD-6 (Vitalograph, Buckingham, UK) [98], or combinations of them, again with a balance of strengths and limitations [99].

A recent development is the use of contemporary FEV_1/FEV_6 devices (PiKo-6 (nSpire, Hertford, UK), COPD-6, *etc.*), so-called microspirometry. Studies are emerging in which measurements performed with these devices (which do not necessarily meet "sufficient standards" for screening spirometry) may have added value when case finding for COPD in primary care, occupational or general population settings usually as an exclusion tool [100, 101].

Regrettably, the rate of false positives is not often reported in population surveys with spirometry, but without conclusive evidence either way, the risks associated with misdiagnosis are minimum, and there is no evidence that elderly individuals with newly identified airflow obstruction or mild COPD are overtreated with respiratory drugs, but merely advised to reduce risk factors, like quitting smoking. Yet the individual and population burden associated with COPD underdiagnosis will remain high for the foreseeable future.

New evidence is coming

Fortunately, the current theoretical debate on the best case-finding strategies [102] will be moved forward by the results of ongoing field studies, such as the TargetCOPD protocol [103] and pragmatic trial [104] (table 2, and figures 4 and 5).

A balancing act of spirometry screening controversies

Some 40 years ago, cardiologists found that high blood pressure, elevated cholesterol, physical inactivity, obesity and tobacco smoking were major risk factors for cardiovascular disease, which was and still is the main cause of death in developed countries. Appropriate large-scale screening and therapeutic programmes combined with encouraging a healthy

Table 2. Ongoing studies/trials aiming to identify better tools and strategies for the case finding of COPD

Name	Reference	Study type	Tools	Inclusion criteria	Study comparison	Size	Setting
TargetCOPD	Published protocol [122]	A pragmatic randomised controlled trial of targeted case finding for COPD *versus* routine practice in primary care: protocol.	Questionnaires	Ever-smoking patients aged 40–79 years, without a current diagnosis of COPD and registered with participating practices.	Active case finding using a postal questionnaire (with supplementary opportunistic questionnaires), and opportunistic-only case finding during routine surgery consultations.	⩾40 000	56 general practices in the West Midlands, UK
A nurse–GP trial	Published protocol [123]	A pragmatic cluster, randomised controlled trial of early intervention for COPD by practice nurse–GP teams					40 general practices in greater metropolitan Sydney, Australia
CECYP	In progress: ClinicalTrials.gov identifier NCT01880177	Developing a COPD case-finding methodology for primary care			COPD-PS ⩾4 and/or PEF ⩽2.2 $L \cdot s^{-1} \cdot m^{-2}$ and full PBD spirometry		
	In progress: ClinicalTrials.gov identifier NCT01576068	COPD case finding in community pharmacies using spirometry					
MARKO	In progress: ClinicalTrials.gov identifier NCT01550679	Early detection of COPD patients in GOLD 0 (smokers) population					
SPIMOAT	In progress: ClinicalTrials.gov identifier NCT01821885	Effectiveness of spirometry as a motivational tool to quit smoking					

GP: general practitioner; CECYP: Cribado de EPOC por Cuestionario y Pico de Flujo; COPD-PS: COPD Population Screener Questionnaire; PEF: peak expiratory flow; PBD: post-bronchodilator; MARKO: Early Detection of COPD Patients in GOLD 0 (smokers) Population; SPIMOAT: Effectiveness of Spirometry as a Motivational Tool to Quit Smoking.

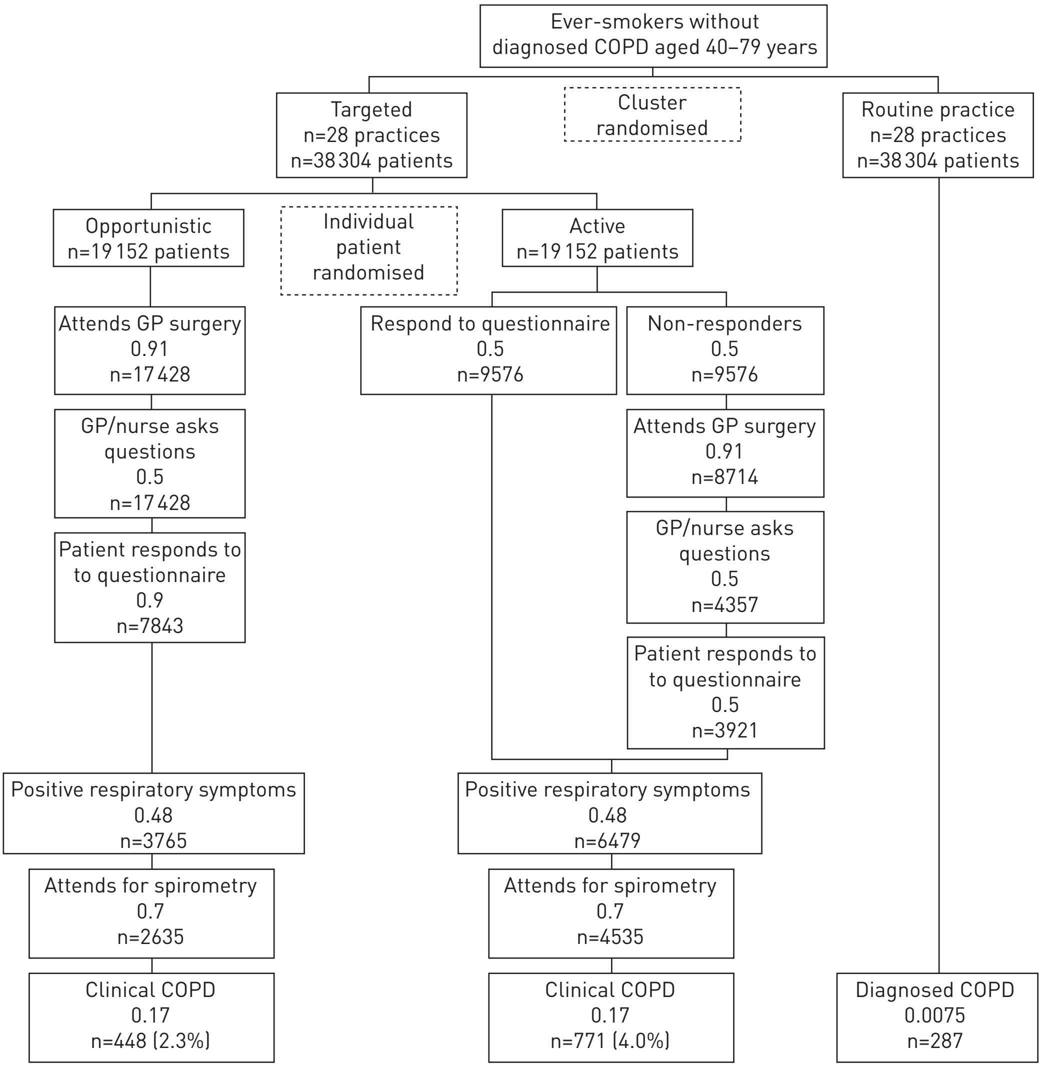

Ever-smokers without diagnosed COPD aged 40–79 years
Targeted n=28 practices n=38 304 patients
Cluster randomised
Routine practice n=28 practices n=38 304 patients
Opportunistic n=19 152 patients
Individual patient randomised
Active n=19 152 patients
Attends GP surgery 0.91 n=17 428
Respond to questionnaire 0.5 n=9576
Non-responders 0.5 n=9576
GP/nurse asks questions 0.5 n=17 428
Attends GP surgery 0.91 n=8714
Patient responds to to questionnaire 0.9 n=7843
GP/nurse asks questions 0.5 n=4357
Patient responds to to questionnaire 0.5 n=3921
Positive respiratory symptoms 0.48 n=3765
Positive respiratory symptoms 0.48 n=6479
Attends for spirometry 0.7 n=2635
Attends for spirometry 0.7 n=4535
Clinical COPD 0.17 n=448 (2.3%)
Clinical COPD 0.17 n=771 (4.0%)
Diagnosed COPD 0.0075 n=287

Figure 4. Target COPD study design. Data are presented as cluster weights, unless otherwise indicated. GP: general practitioner. Reproduced and modified from [103] with permission from the publisher.

lifestyle were implemented on national levels. At that time, there was no evidence that such expensive programmes would reduce morbidity and mortality from cardiovascular disease. However, since then, a steady reduction in death rates from coronary artery disease and stroke has been observed [17]. Regrettably, within the same time period, a rapid increase in prevalence and mortality rates from COPD has been observed in many countries. It may take decades to gain evidence that the early detection of COPD in subjects with a high risk of the disease, conducted in primary care either by the case finding or other method, modifies the burden or the natural history of the disease. However, there are several immediate positive effects of spirometry testing in well-defined, high-risk populations, especially those with a smoking history and symptoms.

All recent COPD guidelines underline the fact that COPD diagnosis has to be confirmed by spirometry [13, 24], but in real life, only 30–50% of newly diagnosed COPD patients are

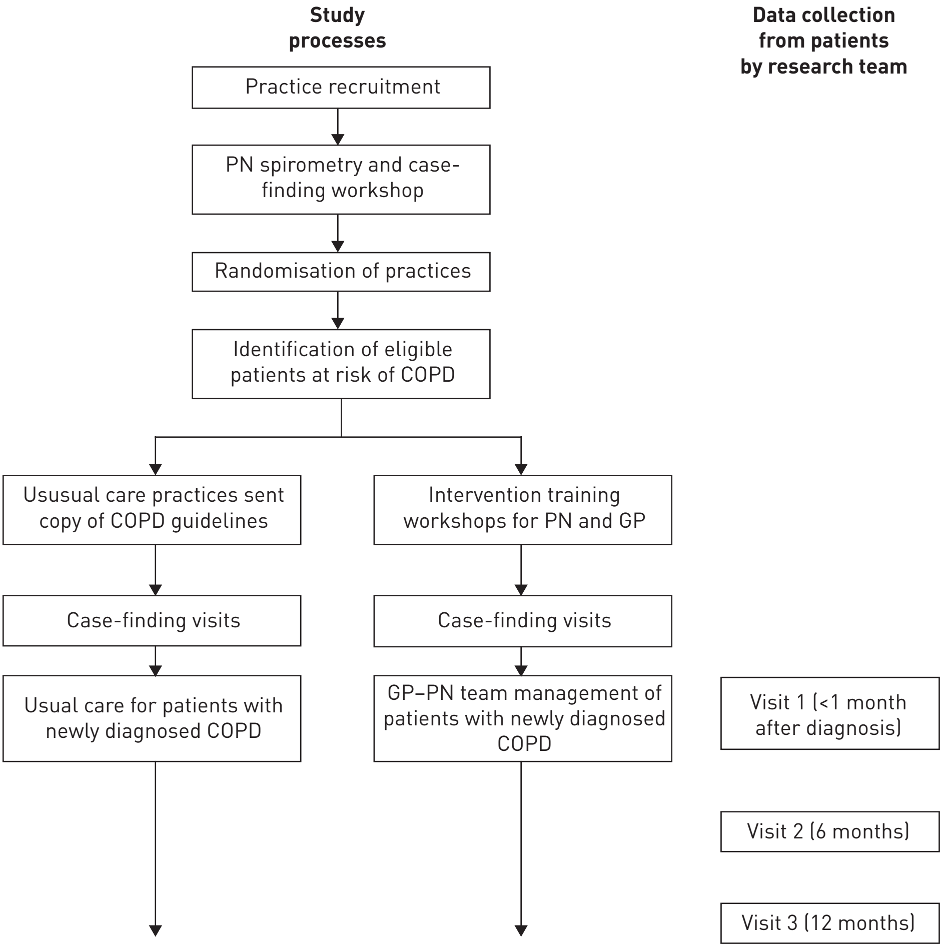

Study processes
Data collection from patients by research team
Practice recruitment
PN spirometry and case-finding workshop
Randomisation of practices
Identification of eligible patients at risk of COPD
Ususual care practices sent copy of COPD guidelines
Intervention training workshops for PN and GP
Case-finding visits
Case-finding visits
Usual care for patients with newly diagnosed COPD
GP–PN team management of patients with newly diagnosed COPD
Visit 1 (<1 month after diagnosis)
Visit 2 (6 months)
Visit 3 (12 months)

Figure 5. Pragmatic trial study design. GP: general practitioner; PN: practice nurse. Reproduced and modified from [104] with permission from the publisher.

confirmed by spirometry [105]. This leads to large mislabelling of respiratory diagnoses. Spirometry testing in patients diagnosed as having COPD or asthma on clinical grounds only, showed that spirometry resulted in a change of diagnosis in ~30% of patients from COPD to asthma and *vice versa* [106], as there are dyspnoeic patients with congestive heart failure treated as COPD patients. A normal spirometry result allows ineffective, and sometimes potentially harmful treatments to be withdrawn. The benefits of appropriate treatment cannot be downgraded.

Underutilisation of spirometry is not only a concern in primary care. Analysis of medical records of patients hospitalised in academic, tertiary-care hospitals showed that only 31% of patients diagnosed as having COPD performed spirometry, in contrast with patients with congestive heart failure, among whom 78% had confirming echocardiography [107]. Early diagnosis using spirometry would facilitate more COPD patients diagnosed and treated according to guidelines. Several studies have shown that patients in moderate stages of COPD usually remain undiagnosed until their disease progresses to more severe stages [108]. This is a large group, comprising 30–50% of the total number of COPD patients. Around 50% of them are symptomatic, experiencing dyspnoea on exertion. Such patients should be treated and they benefit from bronchodilating treatment. Recent large long-term COPD trials included large numbers of subjects with moderate COPD, and resulted in sustained bronchodilatation, an improvement in quality of life, and a reduction in exacerbation rates [109, 110]. Exertional dyspnoea may also be observed in patients with mild COPD [111], resulting in a poorer quality of life and a higher number of missed working days than in subjects with normal spirometry. They should also not be left untreated [112]. The only way to achieve this is by early diagnosis.

Evidence that undiagnosed airflow obstruction has a dose–response gradient for several unspecific adverse health effects (*e.g.* poor/fair general health status, difficulty walking 1⁄4 mile, difficulty lifting or carrying 10 lb, and even requiring help with personal care) when compared with individuals with no airflow obstruction, is demonstrated by the white subjects of ⩾45 years of age in the NHANES III (figure 6) [17].

As previously stated, there is evidence that impaired lung function characterised by reduced FEV1 is a powerful predictor of an increased risk of lung cancer and cardiovascular disease

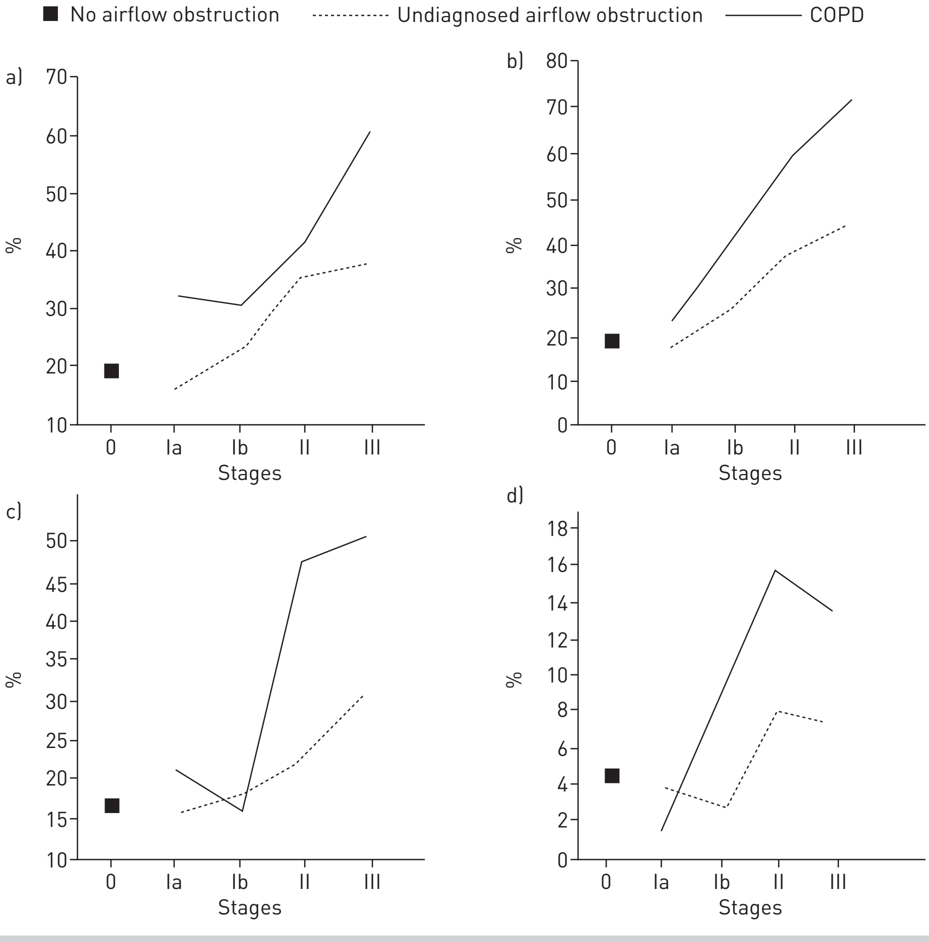


Figure 6. Prevalence of several adverse health effects among participants of the third National Health and Nutrition Examination Survey (NHANES III), with different stages of airflow obstruction. The adverse health effects were: a) poor/fair general health status; b) difficulty walking 1/4 mile; c) difficulty lifting or carrying 10 lb; and d) requiring help with personal care. Reproduced and modified from [17] with permission from the publisher.

[113]. Early diagnosis of COPD would alert attending physicians to assess other potential risk factors, and to introduce primary or secondary prevention of cardiovascular disease.

Spirometric testing even in individuals at high risk of COPD may unveil large numbers of asymptomatic COPD patients. Up to now, smoking cessation is the only intervention that convincingly slows down the progression of the disease. The best health effects in quitters have been found in subjects <50 years of age [114], and actually in the general population the earlier a person quits, the larger the benefits in lung function [54]. Early diagnosis gives a unique opportunity to target that group with the full array of antismoking portfolios. Smoking cessation in patients with COPD is more difficult to achieve than in healthy subjects [115], but inconclusive evidence on spirometry in biomedical risk assessment does not necessarily mean negative evidence. Early diagnosis gives ample time for supporting and helping smokers in their ups and downs until ultimate success in giving up smoking. Perhaps the early diagnosis and smoking cessation programmes for COPD in Finland provide the first evidence of the impact of early diagnosis on the natural history and burden of COPD [64].

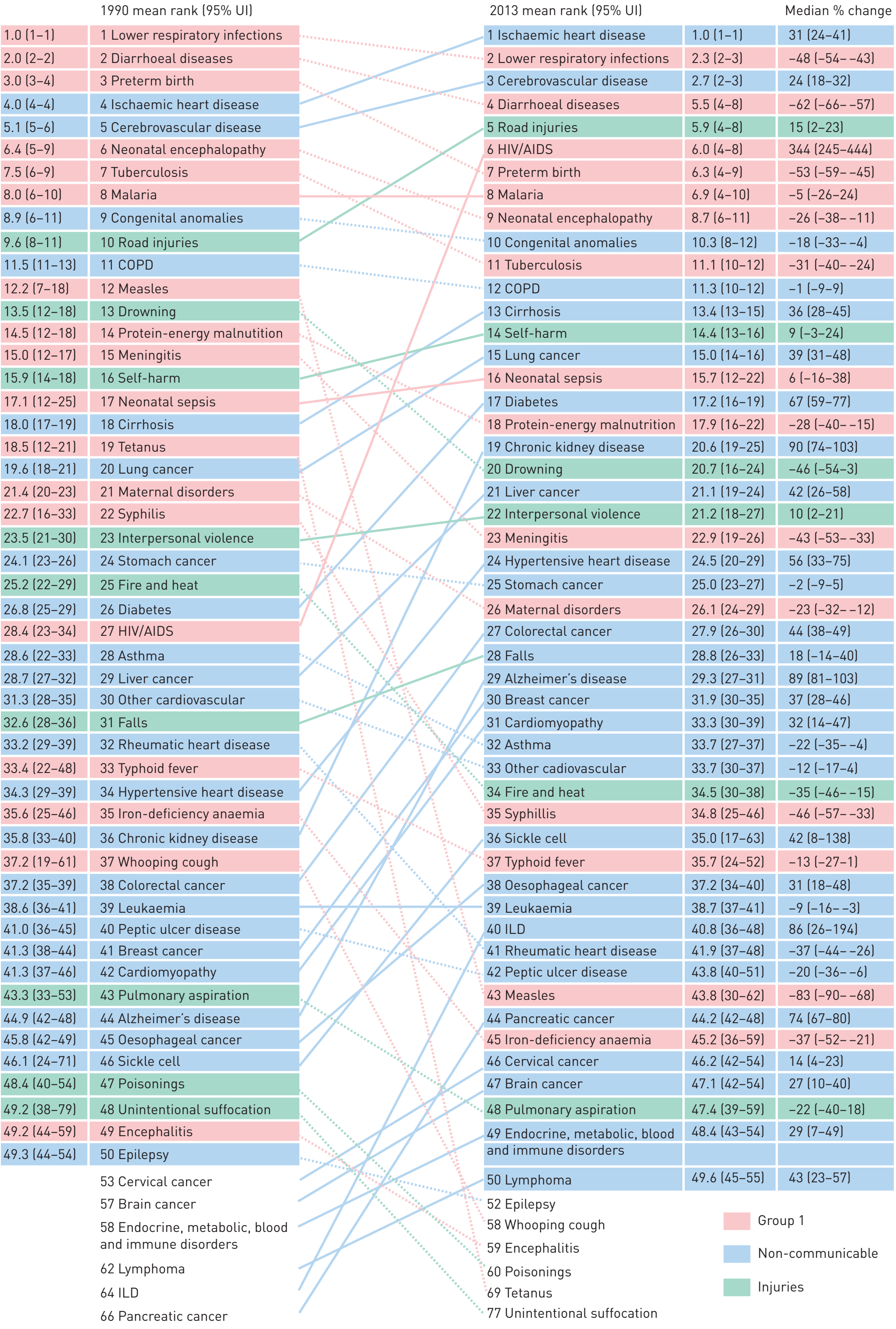
Further information on the potential effects of smoking cessation interventions in newly detected airflow obstruction is available elsewhere [116].

Concluding remarks

Objectively, there has been a recent substantial reduction in death related to COPD in Europe and worldwide. Worldwide, the WHO estimated a decrease of global years of life lost of (figure 7) [1]. In Europe, standardised mortality rates have also decreased in most EU-27 countries [117]. Whether some of these changes are related to wider implementation of spirometry requires further research and confirmation.

Spirometry screening remains a hot topic and there is a secular absence of evidence, with no clarity even on terminology, which adds fuel to the controversy. It is sometimes considered that spirometry programmes designed to detect COPD in the general adult population have a low positive yield and a high false-positive rate. Actually, the yield will depend on the baseline *a priori* risk of the population surveyed. As previously discussed, in those >40 years of age who smoke and do not have a diagnosis of COPD, the yield is approximately one in five, but increases to one in three or better in those who are older, have more exposure to tobacco and/or have respiratory symptoms. This is indeed a better yield than existing screening strategies already established for metabolic disorders, cancer or cardiovascular disorders. Regrettably, the rate of false positives is not often reported in population surveys with spirometry, but we believe, without conclusive evidence either way, that the risks associated with misdiagnosis are minimum, and to our knowledge there is no evidence that elderly individuals with newly identified airflow obstruction or mild COPD are overtreated with respiratory drugs, but merely advised to reduce risk factors, like quitting smoking.

Within our stochastic universe, and in individuals in a state of non-disease (but only at risk of disease), any prevention will surely remain controversial [118]. If the medical profession does not take seriously the early signs of COPD, it is likely that patients will continue to trivialise their condition. For those who are smoking or frequently relapse, this sends the wrong message as we know that their disease will almost certainly progress with continued smoking. An important part of primary care concerns secondary prevention, which involves early detection of disease, as well as monitoring chronic illness. We have a professional duty



1990 mean rank (95% UI)	
1.0 (1–1)	1 Lower respiratory infections
2.0 (2–2)	2 Diarrhoeal diseases
3.0 (3–4)	3 Preterm birth
4.0 (4–4)	4 Ischaemic heart disease
5.1 (5–6)	5 Cerebrovascular disease
6.4 (5–9)	6 Neonatal encephalopathy
7.5 (6–9)	7 Tuberculosis
8.0 (6–10)	8 Malaria
8.9 (6–11)	9 Congenital anomalies
9.6 (8–11)	10 Road injuries
11.5 (11–13)	11 COPD
12.2 (7–18)	12 Measles
13.5 (12–18)	13 Drowning
14.5 (12–18)	14 Protein-energy malnutition
15.0 (12–17)	15 Meningitis
15.9 (14–18)	16 Self-harm
17.1 (12–25)	17 Neonatal sepsis
18.0 (17–19)	18 Cirrhosis
18.5 (12–21)	19 Tetanus
19.6 (18–21)	20 Lung cancer
21.4 (20–23)	21 Maternal disorders
22.7 (16–33)	22 Syphilis
23.5 (21–30)	23 Interpersonal violence
24.1 (23–26)	24 Stomach cancer
25.2 (22–29)	25 Fire and heat
26.8 (25–29)	26 Diabetes
28.4 (23–34)	27 HIV/AIDS
28.6 (22–33)	28 Asthma
28.7 (27–32)	29 Liver cancer
31.3 (28–35)	30 Other cardiovascular
32.6 (28–36)	31 Falls
33.2 (29–39)	32 Rheumatic heart disease
33.4 (22–48)	33 Typhoid fever
34.3 (29–39)	34 Hypertensive heart disease
35.6 (25–46)	35 Iron-deficiency anaemia
35.8 (33–40)	36 Chronic kidney disease
37.2 (19–61)	37 Whooping cough
37.2 (35–39)	38 Colorectal cancer
38.6 (36–41)	39 Leukaemia
41.0 (36–45)	40 Peptic ulcer disease
41.3 (38–44)	41 Breast cancer
41.3 (37–46)	42 Cardiomyopathy
43.3 (33–53)	43 Pulmonary aspiration
44.9 (42–48)	44 Alzheimer's disease
45.8 (42–49)	45 Oesophageal cancer
46.1 (24–71)	46 Sickle cell
48.4 (40–54)	47 Poisonings
49.2 (38–79)	48 Unintentional suffocation
49.2 (44–59)	49 Encephalitis
49.3 (44–54)	50 Epilepsy
	53 Cervical cancer
	57 Brain cancer
	58 Endocrine, metabolic, blood and immune disorders
	62 Lymphoma
	64 ILD
	66 Pancreatic cancer

2013 mean rank (95% UI)		Median % change
1 Ischaemic heart disease	1.0 (1–1)	31 (24–41)
2 Lower respiratory infections	2.3 (2–3)	−48 (−54– −43)
3 Cerebrovascular disease	2.7 (2–3)	24 (18–32)
4 Diarrhoeal diseases	5.5 (4–8)	−62 (−66– −57)
5 Road injuries	5.9 (4–8)	15 (2–23)
6 HIV/AIDS	6.0 (4–8)	344 (245–444)
7 Preterm birth	6.3 (4–9)	−53 (−59– −45)
8 Malaria	6.9 (4–10)	−5 (−26–24)
9 Neonatal encephalopathy	8.7 (6–11)	−26 (−38– −11)
10 Congenital anomalies	10.3 (8–12)	−18 (−33– −4)
11 Tuberculosis	11.1 (10–12)	−31 (−40– −24)
12 COPD	11.3 (10–12)	−1 (−9–9)
13 Cirrhosis	13.4 (13–15)	36 (28–45)
14 Self-harm	14.4 (13–16)	9 (−3–24)
15 Lung cancer	15.0 (14–16)	39 (31–48)
16 Neonatal sepsis	15.7 (12–22)	6 (−16–38)
17 Diabetes	17.2 (16–19)	67 (59–77)
18 Protein-energy malnutrition	17.9 (16–22)	−28 (−40– −15)
19 Chronic kidney disease	20.6 (19–25)	90 (74–103)
20 Drowning	20.7 (16–24)	−46 (−54–3)
21 Liver cancer	21.1 (19–24)	42 (26–58)
22 Interpersonal violence	21.2 (18–27)	10 (2–21)
23 Meningitis	22.9 (19–26)	−43 (−53– −33)
24 Hypertensive heart disease	24.5 (20–29)	56 (33–75)
25 Stomach cancer	25.0 (23–27)	−2 (−9–5)
26 Maternal disorders	26.1 (24–29)	−23 (−32– −12)
27 Colorectal cancer	27.9 (26–30)	44 (38–49)
28 Falls	28.8 (26–33)	18 (−14–40)
29 Alzheimer's disease	29.3 (27–31)	89 (81–103)
30 Breast cancer	31.9 (30–35)	37 (28–46)
31 Cardiomyopathy	33.3 (30–39)	32 (14–47)
32 Asthma	33.7 (27–37)	−22 (−35– −4)
33 Other cadiovascular	33.7 (30–37)	−12 (−17–4)
34 Fire and heat	34.5 (30–38)	−35 (−46– −15)
35 Syphillis	34.8 (25–46)	−46 (−57– −33)
36 Sickle cell	35.0 (17–63)	42 (8–138)
37 Typhoid fever	35.7 (24–52)	−13 (−27–1)
38 Oesophageal cancer	37.2 (34–40)	31 (18–48)
39 Leukaemia	38.7 (37–41)	−9 (−16– −3)
40 ILD	40.8 (36–48)	86 (26–194)
41 Rheumatic heart disease	41.9 (37–48)	−37 (−44– −26)
42 Peptic ulcer disease	43.8 (40–51)	−20 (−36– −6)
43 Measles	43.8 (30–62)	−83 (−90– −68)
44 Pancreatic cancer	44.2 (42–48)	74 (67–80)
45 Iron-deficiency anaemia	45.2 (36–59)	−37 (−52– −21)
46 Cervical cancer	46.2 (42–54)	14 (4–23)
47 Brain cancer	47.1 (42–54)	27 (10–40)
48 Pulmonary aspiration	47.4 (39–59)	−22 (−40–18)
49 Endocrine, metabolic, blood and immune disorders	48.4 (43–54)	29 (7–49)
50 Lymphoma	49.6 (45–55)	43 (23–57)
52 Epilepsy		
58 Whooping cough		
59 Encephalitis		
60 Poisonings		
69 Tetanus		
77 Unintentional suffocation		

Figure 7. Top 50 causes of death in 1990 and 2013. Reproduced and modified from [1] with permission from the publisher.

to diagnose early and monitor various conditions without actively treating them, except with lifestyle advice (*i.e.* arterial hypertension, dyslipidaemia, hyperglycaemia, *etc.*). Comprehensive population screening could be achieved by programmes linking spirometry screening to other established screening procedures, such as hypertension screening, cervical smears or mammography in women, or bowel cancer or diabetes screening in both sexes.

People who leave a job because they have respiratory symptoms related to work are likely to be screened and identified in a case-finding programme. Near the retirement age of working populations, annual check-ups including spirometry might be an excellent opportunity for lung function screening.

In the case of early COPD, once detected by screening, these individuals can be offered smoking-cessation advice repeatedly and may benefit from other measures. Repeated testing should also allow earlier recognition of progression to a more serious level of disease requiring medical intervention. Increased collaboration of chest with primary care and internal medicine physicians is fundamental. Echoing a clinicians' viewpoint, guidelines should be advisory to clinicians for the management of COPD patients, and not dominated by epidemiologists' or physiologists' concerns that an overdiagnosis of COPD will be the outcome of screening elderly smokers or nonsmokers [119].

The spirometer is to COPD as the sphygmomanometer is to hypertension, and both tools help in smoking cessation. A wider implementation of quality spirometry should help to reduce the future COPD burden.

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Chapter 2

COPD as a consequence of premature birth?

Charlotte E. Bolton

Case history: A 40-year-old woman is newly diagnosed with COPD in the UK. The degree of airflow obstruction appears severe for her age and smoking history. She does not have α_1-ATD, has smoked only tobacco and has not had significant passive smoke exposure. On direct questioning, she tells you that she was born at 32 weeks gestation and with low birth-weight. How might this have impacted her risk of developing airflow obstruction?

Chapter summary: There is an increasing awareness of the longer-term respiratory sequelae of being born premature. With publications reporting a chronic obstructive airways pattern and an increased susceptibility to respiratory infections and hospitalisations, is this a cause of COPD? With about 8% of births being preterm (<37 weeks of gestation) and survival improving, there are important respiratory implications. This chapter will discuss the available literature on the respiratory state of adults born preterm and consider whether this can be regarded as COPD. It will also highlight many important gaps in our understanding.

The evidence that respiratory disease in adult life may in part stem from early life factors that affect lung development has grown considerably over the years. Early life factors were associated with impaired lung function and increased risk of COPD by Svanes *et al.* [1] in the European Community Respiratory Health Survey follow-up study and accumulative in their respiratory impact. There, factors included exposure to parental smoking, childhood infections and parental asthma. Demonstration of the association of childhood to later development of obstructive airways disease infections dates back, much earlier, to 1977 [2]. Comprehensive reviews of early lung development on respiratory health and disease in general has been covered elsewhere [3]. This chapter focuses on preterm birth.

Being born premature not only has immediate respiratory consequences but there is increasing evidence of later lung function impairment and symptoms in childhood and in adulthood [4, 5]. Studies suggest this is an obstructive picture, with some or no reversibility, an emphysematous appearance on imaging [6] and symptoms not unlike those with COPD [4]. Many of the studies report the means of the population and a pertinent gap in our knowledge is who is affected and if any gradation in abnormalities across the population. This has therefore led to consideration of whether preterm birth is a cause of

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COPD. Linked with this is the understanding that not every smoker develops COPD [7] and that chronic lung disease is likely to develop from both host factors, such as early lung development, and genetics as well as environmental factors such as tobacco smoke. Whilst there is recognition of accelerated decline in lung function with tobacco smoke exposure, the failure to achieve maximal potential in lung development in childhood can impact on adult lung function too (figure 1) [9, 10]. Evolving neonatal care has permitted a far better neonatal survival of preterm babies including those born very preterm (⩽32 weeks gestation) and those born extremely preterm (⩽28 weeks gestation) [11, 12]. The later survival of these infants has also improved significantly [13–15] and a majority is now reaching adulthood, amassing a large "at-risk" population [16, 17].

Lung development

In order to set the scene, normal lung development *in utero* occurs through the stages of embryonic, pseudoglandular, canalicular and saccular phases, which have been described in detail previously [18–20]. Although the airways branching system is laid down early on during the pseudoglandular phase, the development of gas exchanging areas is much later during the saccular phase and then alveolarisation starting from 36 weeks onwards until and after delivery. Contrary to the traditional perspective, recent work using hyperpolarised ^{3}He MRI has demonstrated that alveolar numbers continue to increase after birth during childhood and adolescence [21, 22].

Throughout childhood, the lungs grow with an increase in both spirometric parameters of FEV_1 and FVC, reaching a plateau around the age of 20–25 years old. Lung function appears to "track" throughout childhood [23], such that being in the lower quartile for lung function in infancy is associated with worse lung function in young adulthood. From this young adult plateau, there is then a steady decline in lung function measures such as the FEV_1 and FVC throughout adulthood. However, the subsequent decline trajectory can be worsened by a variety of insults such as tobacco smoke.

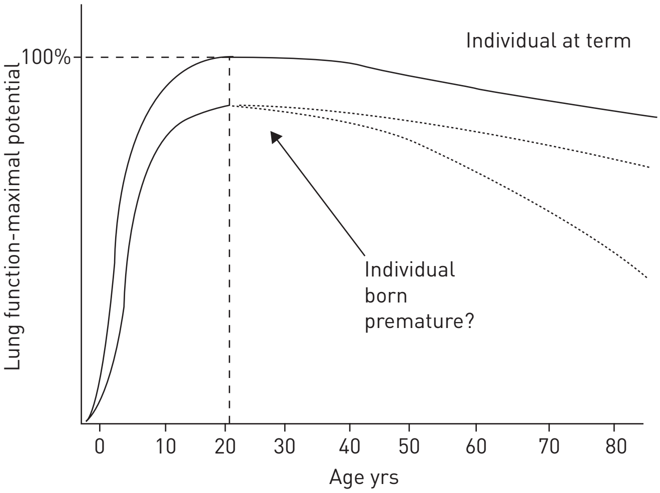

Figure 1. The failure to achieve maximal potential in lung development in childhood can impact on adult lung function. Reproduced and modified from [8] with permission from the publisher.

Preterm birth

Across Europe, there is some variation but roughly 5.5–11.1% of all live births are preterm [12, 24]. The immediate consequences of a preterm birth on lung development are twofold: the alveoli are less mature and the surfactant-deficient premature lung is exposed to the variety of required treatments including insults to the immature, such as positive pressure ventilation and hyperoxia. Even room air is hyperoxic compared with the fetal environment). Over recent years, there has been a transformational change in the nature of neonatal care delivered encompassing less intubation and lower pressures, as well as inhaled surfactant and also antenatal steroids to the mother. The changes in neonatal care together with the opportunity to salvage more extremely preterm infants have altered any immediate lung impairment from the traditional description of bronchopulmonary dysplasia (BPD) to "new" BPD, which more relates to alveolar arrested development. There are infants who develop BPD due to their prematurity and have not had prolonged ventilator support. A working classification for the term new BPD is according to use of supplemental oxygen at or beyond 36 weeks postconception [25, 26]. Whilst the nature of BPD might have changed, there is still a significant proportion with BPD.

The tradition has been for these infants to be followed up for a couple of years during and just after any period of supplemental oxygen requirement but then be discharged by paediatricians respiratory-wise with no systematic monitoring during childhood. Children born preterm develop more respiratory problems than term-born children, irrespective of whether or not they had BPD but may well present with these symptoms to a non-specialist [27–30]. Many children have clinically significant lung function impairment and there is greater respiratory infection susceptibility [27, 31–33]. Often these symptoms will be labelled as asthma by virtue of a wheezy, breathless child but this is a diagnostic term needing particular clarification in these individuals born premature, as will be discussed later [34, 35].

What is apparent is the fact that although more children are surviving earlier and earlier preterm births and then reaching adulthood, as respiratory physicians we are not encompassing key information in our history taking regarding a premature birth, neonatal care or birth weight [36, 37]. A survey of members of the British Thoracic Society identified that only a small minority ask "most respiratory patients" about early life factors. Those that did were largely paediatricians and the vast majority of respondents did not ask at all. If consideration of these key early life events is not made, then the potential contribution to the current status will not be made. A further concern is attaining correct information back from the respondent. Whilst paediatric consultations will often include the personal child health record and also the parents are accompanying the child know information, the current system does not set itself up well to support a young adult in offering this information to their healthcare professional. The evolution of electronic records should be of immense value here.

Respiratory outcomes in adults born preterm

Amongst adults, a number of studies have reported outcomes, across the range of symptoms, diagnosis, lung function and exercise capacity, imaging and healthcare resources. Of particular note, however, is that the studies have mostly been in small groups of adults, across a wide age range and hence across a diverse range of neonatal care and almost all in the pre-surfactant era. Two systematic reviews, one in children and adults on lung function and one on general and respiratory outcomes in adults who had BPD, have been published [4, 5]. One further challenge is untangling the consequences of the preterm birth from the likely cause of the preterm birth in first place which may also impact on lung development. Maternal smoking and infection are influential factors impairing *in utero* lung development [38–40].

Symptoms

Vrijlandt *et al.* [41] reported increased respiratory symptoms, in particular breathlessness, in 19-year-old adults born very premature compared with controls. The index cases here were born in 1983 at <32 weeks gestation and/or <1500 g birth weight. Amongst females, respiratory symptoms in general were more common and wheezing in the past 12 months was also a feature but interestingly not in males. Other studies, largely confirming the difference in respiratory symptoms between those born preterm and term controls are presented in the systematic review by Gough *et al.* [4].

Gough *et al.* [42] went on to study 72 adults born preterm with BPD, 57 born preterm without BPD and 78 term controls as part of the Premature Adult Lung Study (PALS). The babies born preterm were born over a 15-year period from 1978 to 1993. The controls were sex and birth-date matched to the preterms with BPD, born term in the same hospital. The adults with BPD were far more likely to describe wheeze, breathlessness and be classed as “symptomatic” on the “European Community Respiratory Health Survey” score compared with the term controls. Furthermore, the BPD preterm group had an odds ratio (95% CI) of 2.86 (1.14–7.16), more likely to report wheeze compared with the non-BPD preterm group.

Reported diagnoses and healthcare resources

Several studies have enquired about respiratory physician diagnoses with far greater prevalence of asthma diagnosed in those born preterm compared with term controls [41–43]. Gough *et al.* [42] reported that 40% of young preterm-born adults had a previous physician-diagnosis of asthma. Ever diagnosis of asthma, current doctor diagnosis of asthma, hospitalisation for airway respiratory problem and inhaler use were all greater in the preterms compared to term controls in the study by Halvorsen *et al.* [44]. Filippone *et al.* [45] raise caution of the mislabelling as asthma. A physician-reported diagnosis of COPD in these studies was not a prominent finding; however, these were select recruitment of known subjects who had been born preterm and often at very early adulthood. It does not allow for what diagnosis may be made in a general respiratory clinic, especially if the physician is unaware of the neonatal challenges.

Two separate studies by Walter and co-workers [46, 47] detail increased risk of hospitalisation for respiratory cause in young adults born with a low birthweight. One was a population-based case–control study based on discharges of people with a respiratory illness over the age of 18 years old [47]. The other was a retrospective cohort study based on birth certificates [46].

Lung function

There have been a number of studies reporting lung function in adults born preterm [42, 44, 48–51] and many encompassed in systematic reviews [4, 5]. These have largely centred on spirometric measures. Narang *et al.* [49] followed up a group of people born preterm and reported at 21 years of age that, although symptoms were worse than term controls, there was no persisting airways obstruction or hyperresponsiveness, suggesting a degree of catch-up. The cases here were young adults born <37 weeks, with a median gestation of 31.5 weeks, who had been followed up from birth. Other studies however have demonstrated worse spirometry in young adulthood in those born preterm: including those born extremely preterm [44, 48]; those who had BPD [42, 44]; those with very low birth weight [50] and preterm alone [51]. Over time, there is some evidence that the lung function of survivors of BPD is improving however remains an important cause of morbidity to this ever growing sized at-risk population [5]. But again, these lung function outcomes encompass individuals born pre-surfactant and before the modern era of neonatal care. Whilst there is some short-term acute bronchodilator reversibility in airways obstruction, as presented in a systematic review [52] (though largely the studies are in children), studies, again performed in children born preterm, suggest that the airflow obstruction is not classically responsive to ICSs nor portrays classical asthma-like inflammation [34, 44, 53].

The Avon Longitudinal Study of Parents and Children had lung function measures in younger and older childhood (14–17 years old). Here, even late preterm (33–34 weeks gestation) subjects had impaired small airways lung function [54]. The significance of this is that the number of babies born late preterm far outweighs those born very preterm.

What happens to lung function during adulthood in these individuals? Is there a steeper decline? VOLLSAETER *et al.* [55] report parallel tracking of the impaired lung function from adolescence to young adulthood in a small group of people born ⩽28 weeks gestational age or ⩽1000 g birth weight born in one area of Norway. This was evident in both those with a history of BPD and those without – but more pronounced impairment in those with former BPD. Although people born preterm are often risk-averse [56–58], smoking is common [49] and therefore may impact synergistically with other respiratory insults [59] to affect the trajectory of lung function change throughout adulthood.

Other lung function measures have been explored to a lesser degree. There was evidence of impaired gas transfer in those born preterm compared with term controls [51, 60]. This supports the studies in those born extremely preterm from the "EPICure" cohort at the age of 11 years old [61] in which gas trapping and ventilation inhomogeneity were also seen [33]. Although some studies report increased positive methacholine responsiveness in adults born preterm [43, 44] this is not universally reported [49]. In a recent paper by VOLLSAETER *et al.* [62] among adults born extremely preterm, methacholine responsiveness was greater than term controls. Exercise capacity appears suboptimal in those adults born preterm [51, 63, 64] with a number of factors proposed to contribute to the limitation, not just ventilation.

Imaging

A few studies report in small-sized groups of adults born premature the results of lung imaging, in particular based on CT scans. WONG *et al.* [6] reported the CT appearances in 21 young adults born premature, characterised that all had moderate-to-severe BPD at one institution between 1980 and 1987. In all of the 19 consenting for a CT scan, there were CT abnormalities; with the most common abnormality (16 out of 19) being what was described as an emphysema picture, mostly centrilobular. This was quantified based on the proportion of lung voxels of low density using Hounsfield Units. The volunteers were largely non-smokers, with two having a <1 pack-year history. The severity of the emphysematous appearance was related to severity of spirometry; be it the FEV_1 or $FEF_{25-75\%}$. However, the lack of controls is a limiting factor. The same group went on to report CT findings of 51 adult survivors of BPD in general, this time with an emphysematous picture reported in 47% but overall 50 out of 51 had an abnormal picture with other changes including triangular opacities, linear opacities and gas trapping [65].

Aukland *et al.* [66] scanned 74 people: 32 children (aged 10 years old, born 1991–1992) and 42 young adults (aged 18 years old, born 1982–1985), all of whom had been born $\leqslant$28 weeks gestation. Using HRCT scanning, abnormalities were reported in 63 out of 74 subjects. Here, the most common abnormalities were linear and triangular opacities, gas trapping and a mosaic perfusion with a mean HRCT score of 3.6 (range 0–13) (out of a maximum potential score of 50), higher in those aged 18 years compared with the 10 year olds. Those with a history of BPD had a higher mean HRCT score and greater linear and triangular opacities, gas trapping and mosaic perfusion. Emphysema was not a particular issue reported. Aquino *et al.* [67] reported that 24 out of 26 people who were born preterm and had BPD with a median gestational age of 28 weeks had CT abnormalities. The age range was from 5 to 18 years with a mean age of 10 years. Reticular opacities (n=22), architectural distortion (n=18), decreased density (n=20) and air trapping on expiratory films (n=24) were key features.

A further prospective study also reported that CT abnormalities were common in people who had BPD: 24 out of 26 had abnormal scans. Although it included adolescents, the median age was 10 years old [67]. Generally however, all these imaging studies lack term control data for comparison and the cases were born in the era of old BPD.

Is it COPD?

Taken together, there appears to be considerable respiratory morbidity in a growing adult population who were born preterm. Many of these individuals may well present in childhood or young adulthood with respiratory symptoms; some may present later on. They will not have been under long-term paediatric follow-up and unless a neonatal history is specifically requested and considered, any possible link to being preterm will be missed [36, 37]. It is likely that the spirometry presentation is of airflow obstruction and may have some reversibility. Furthermore, they present with exertional breathlessness and wheeze. So, is this an early COPD? A significant lack of evidence and research in this area prevents any comprehensive answer. Some, by nature of how common the condition is, will have asthma. Others may have a historical or current diagnosis of asthma made by virtue of a cocktail of respiratory symptoms, age and evidence of airflow obstruction, and this needs addressing. Some adults will have COPD with a traditional aetiological background [68]. But is chronic airflow obstruction and persisting symptoms in an individual born preterm and without a known an environmental factor or α_1-ATD, COPD? Fundamental key areas that future research must address include identifying the nature of the airflow obstruction: is it an inflammatory contribution (and if so, what) or whether these are fixed developmental structural changes. This has significant implications such that the inadvertent “COPD” (or asthma) label does not lead to an escalation of inappropriate therapies resulting in huge cost, side-effect and in-effectiveness by aiming to treat the wrong condition. However, this does not prevent general respiratory lifestyle recommendations, such as smoking cessation, maintaining exercise regime, influenza vaccination and nutritional optimisation to be discussed and implemented.

Other key research areas needed include regarding whether individuals born preterm should be screened and whether particular groups are at particular risk; what the best lung function tests are to identify the impairment, proportion with a respiratory impairment (as opposed to lower lung function mean data in a preterm group compared to control population); what the trajectory of change is in adulthood and whether further insults add synergistically and lastly randomised controlled trials of therapeutic intervention based on a better mechanistic understanding so that focussed therapies can be developed. In the meantime, caution in labelling these individuals as COPD must remain. Such labelling could lead to automatic routing of management for a condition generally linked to tobacco or other environmental exposure and is based on a number of assumptions that will not necessarily improve symptoms and may add to the respiratory burden through their side-effects.

In summary, there is a requirement to educate and integrate a former neonatal history, not just in the paediatric clinics but in adult respiratory clinics such that symptoms and lung function do not lead to a "convenient" diagnosis [36, 37]. Attaining accurate information regarding these neonatal events, particularly in the adult clinic, remains a challenge. The review of the literature flags up not just gaps, but chasms, in our understanding that must be prioritised in future research in order to offer effective management options [69, 70]. Whilst studies have highlighted some of the issues associated with respiratory health of those born preterm, this is really just the first step and it is far too soon to clump this condition with COPD in general.

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Chapter 3

Nonsmokers and biomass exposure

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Case history: A 75-year-old female from a rural area of Oaxaca, Mexico, reported cough and phlegm for >30 years, exertional breathlessness for 4 years and wheezing during the winter. She reported suffering from frequent respiratory infections during childhood and adolescence. The patient had cooked with wood smoke for >50 years. As a child, she helped her mother with housework, spending time in an unventilated, smoky kitchen for long periods of time. She reported no history of tobacco smoking. She is illiterate and has a very low income. The patient is overweight and presented to the COPD clinic with a moderate increase of cough, green sputum and dyspnoea. Spirometry showed an FEV_1 of 65% predicted and an FEV_1/FVC of 66. Oxygen saturation at rest was 85% and the CT showed air trapping. Is this chronic asthma, ACOS or COPD?

Chapter summary: This chapter addresses COPD causes beyond smoking, with emphasis on COPD associated with biomass (BE-COPD). Most of the information obtained from meta-analyses that focus on risk factors of COPD in nonsmokers points out that biomass is the main cause of COPD. Almost 50% of deaths from COPD in developing countries may be attributed to biomass; ~75% of these deaths are reported in women. There are clinical differences between BE-COPD and COPD associated with tobacco smoke (TE-COPD). In contrast to smokers, these subjects mainly have the chronic bronchitis phenotype. Air trapping predominates on CT and necropsy demonstrates more severe bronchiolitis. However, lung function, exercise capacity and molecular inflammation are similar, as are comorbidities. Information relating to genetic causes, pathogenesis and treatment is scarce. Current evidence suggests that further research is needed on this topic.

Tobacco smoking is the most common and best known cause of COPD [1]. But it is not the only cause of COPD. Increasing evidence suggests that an important number of subjects with COPD are never-smokers [2]. The prevalence of COPD among nonsmokers shows significant variation across geographic regions and between epidemiological studies. Such variation may be the result of several different aspects, including study design, definition of COPD, diagnostic criteria (spirometrically confirmed Global Initiative of Chronic Obstructive Lung Disease (GOLD) COPD *versus* self-reported COPD), age and sex

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distribution of the studied population [3], the presence of risk factors (second-hand smoke, tuberculosis, indoor air pollution, *etc.*) other than smoking [4, 5], and socioeconomic status. A study by SALVI and BARNES [6] showed that the proportion of nonsmoking-related COPD cases amongst all cases of the disease ranged from 17.0% in Venezuela to 68.6% in India, depending on the diversity of the studied population and the definition of COPD. The proportion appears higher in developing countries and lower in developed countries. Data from the Burden of Obstructive Lung Disease (BOLD) study showed that 28% of COPD cases (from mild to very severe GOLD stages) occurred in never-smokers [7]. In an epidemiological survey of COPD conducted in China, the prevalence of COPD (according to GOLD diagnostic criteria) was 5.2% among nonsmokers aged ⩾40 years [8] and represented 38.6% of all COPD patients [9].

A consistent level of COPD prevalence amongst nonsmokers has been reported in the USA using the National Health and Nutrition Examination Survey (NHANES) III data [10]. Risk factors in nonsmokers may include outdoor air pollution, genetic factors, asthma, occupational exposure and respiratory infection, among others. Table 1 presents a summary of some of the meta-analyses of risk factors associated with COPD in nonsmokers [2, 6, 11–19]. Biomass exposure showed higher odds ratios in a variety of publications [6, 11–13].

Biomass as an indoor air pollution cause of COPD in women

Every year, indoor air pollution from cooking with solid fuels is responsible for >1.5 million deaths due to pneumonia, chronic respiratory disease and lung cancer [20]. Biomass fuels account for 2.9% of all deaths per year worldwide and 3.7% of the overall disease burden in developing countries [21]. In India, 400 000 to 2 million premature deaths occur every year due to indoor air pollution, with the majority of these deaths occurring in children <5 years of age due to acute respiratory infections [21–24]. There is also strong evidence of the impact on women, with reports of up to 34 000 deaths resulting from chronic obstructive disorders [20].

The percentage of people using solid fuels varies widely between countries and regions, and in rural areas ~30–75% of households use biomass fuels for cooking [21, 24, 25]. Solid fuels produce extremely high levels of indoor air pollution. Typical 24-h levels of PM_{10} (particles with a 50% cut-off aerodynamic diameter of ⩽10 μm) in biomass-using homes in Latin America range 300–3000 $\mu g \cdot m^{-3}$ [20]. During cooking, it may peak as high as 10 000 $\mu g \cdot m^{-3}$ [26]. This is in contrast to the standard annual mean PM_{10} levels in outdoor air which were set at 50 $\mu g \cdot m^{-3}$ by the US Environmental Protection Agency (EPA) [27]. The health impact of biomass smoke containing high concentrations of particulates and other pollutants can be devastating, because for every 20 $\mu g \cdot m^{-3}$ increase of PM_{10} in ambient air over the standard, a 1% increase in total daily mortality occurs [27]. Most people are aware of the damaging effects of outdoor air pollution; however, few know that indoor air pollution can be an even greater risk to their health [6, 11–13, 17, 18, 28, 29]. Globally, almost 50% of COPD deaths in developing countries could be due to biomass, with ~75% of these occurring in women. Studies have shown that women exposed to indoor smoke are three times more likely to suffer from COPD, chronic bronchitis or emphysema than women who cook with electricity, gas or other cleaner fuels [2]. A study from Colombia found that use of a biomass stove use for ⩾10 years was associated with a greater risk of COPD (GOLD stage I or greater; OR 1.5 (95% CI 1.22–1.86)) [30]. COPD associated with indoor air pollution from biofuels is now considered to be a sex-specific

Table 1. Meta-analyses of risk factors associated with COPD in nonsmokers

First author [ref.]	Year	Studies n	Study type	Causes	Risk factor	Risk OR (95% CI)
Salvi [6]	2009	NA	Review	Indoor air pollution	BSE	OR range 2.3–6.6
Kurmi [11]	2010	14	Meta-analysis	Indoor air pollution	BSE	2.96 (2.01–4.37)
Hu [12]	2010	9 CCS	Meta-analysis	Indoor air pollution	BSE	2.77 (1.80–4.27)
Po [13]	2011	5 CCS, 1 cohort	Meta-analysis	Indoor air pollution	BSE	2.40 (1.47–3.93)
Eisner [2]	2010	12 CCS	Meta-analysis	Indoor air pollution	ETS	1.56 (1.40–1.74)
Hooper [14]	2012	1 cohort	NA	Indoor air pollution	ETS	1.24 (1.05–1.47)
Hart [15]	2012	NA	Review	Occupational exposures	Diesel exhaust	1.90 (1.3–3.0)
Diaz-Guzman [16]	2012	NA	Review	Occupational exposures	Organic dust	OR range 1.53–2.62
Cai [17]	2014	5 CCS	Meta-analysis	Outdoor air pollution	PM_{10}	1.31 (1.05–1.64)
Allwood [18]	2013	3	Review	Infectious diseases	*M. tuberculosis*	OR range 1.37–2.94
Calligaro [19]	2015	4	Review	Infectious diseases	HIV	1.47 (1.01–2.13)

NA: not applicable; BSE: biomass smoke exposure; CCS: case–control study; ETS: environmental tobacco smoke; PM_{10}: particles with a 50% cut-off aerodynamic diameter of ⩽10 μm; *M. tuberculosis*: *Mycobacterium tuberculosis*.

disease, one that almost solely affects women. It could also be considered to be a public health issue, with double significance: it only affects women and increasing numbers of women are being affected worldwide [31].

As girls in the developing world spend more time with their mothers and help them with domestic work at a very early age, they may be more susceptible to developing respiratory symptoms because they have been exposed to biofuels for ⩾40–50 years [6]. In the case of COPD associated with biomass (BE-COPD), chronic insult beginning in childhood may act as an early stimulus that affects airway structure and function. Some studies suggest that lower respiratory tract infection during childhood is a risk factor for developing chronic airway obstruction in adulthood [29].

Is it COPD or COPD-like disease? Considering the clinical picture and lung function

According to the GOLD statement, there are three characteristics that define COPD: 1) persistent airflow limitation, which is usually progressive; 2) the presence of an enhanced chronic inflammatory response in the airways and the lung; and 3) the presence of comorbidities [32]. The following discussion will use a comparative analysis of these characteristics and the traditional definition of COPD associated with tobacco smoking.

Table 2 presents a comparison of the functional characteristics and clinical variables of BE-COPD and COPD associated with tobacco smoke (TE-COPD). Studies have demonstrated that airflow obstruction is a characteristic of women exposed to biomass [33–36]. In BE-COPD, a greater proportion of subjects with FEV1 limitation are in a less severe group than smokers [37–39]. They also have a reduced *D*LCO, which is milder than that observed in smokers and has a normal or near-normal *D*LCO/alveolar volume ratio [38, 40].

Hyperresponsiveness to methacholine (HRB) challenge is another trait of COPD [41]. Interestingly, women with BE-COPD may react at lower concentrations of methacholine despite having reduced airway obstruction (FEV1) [42] in comparison with smokers [43]. In this sense, HRB in women with BE-COPD may be more severe than in TE-COPD. This could be the cause of the common presence of wheezing.

Although nonspecific HRB may be a risk factor for the development of COPD in women exposed to biofuels, an alternative explanation is that HRB and COPD are independent outcomes. Another hypothesis is that airflow obstruction and bronchial remodelling precede and are causally associated with HRB [44].

The apparent benign low decline in FEV1 in biomass smoke

BE-COPD seems to be an entity in which, in terms of severity and activity, both impairment and progression are lower than that observed in smokers. Accordingly, the time-course behaviour of FEV1 in a Mexican cohort of patients with BE-COPD or TE-COPD during a 15-year follow-up period showed that the rate of FEV1 decline was significantly slower and more homogeneous in BE-COPD patients than in TE-COPD patients (figure 1) [37]. The proportion of rapid decliners in BE-COPD patients was very low (1%) compared with the 11% seen in patients with TE-COPD [37].

Table 2. Comparison of COPD associated with biomass (BE-COPD) and COPD associated with tobacco smoke (TE-COPD)

Characteristics	TE-COPD	BE-COPD	p-value
Subjects n	302	112	
Illiterate patients	52 (17)	104 (93)	<0.001
Females	80 (26.49)	97 (86.61)	>0.001
Age years	68±9	73±9	<0.001
BMI kg·m^{-2}	25±4	27±5	0.014
Tobacco index packs·year^{-1}	57±32		
Biomass index hours·year^{-1}		234±122	
FEV$_1$ post-bronchodilator mL	1255±433	1030±297	<0.001
FEV$_1$ post-bronchodilator %	50±18	63±20	<0.001
Reversibility %	12 (5–20)	10 (0.4–18)	0.076
P_{aO_2} mmHg	59±13	54±9	0.008
P_{aCO_2} mmHg	33±6	35±5	0.169
S_{aO_2} %	89±7	87±5	0.132
6MWT m	360 (225–450)	312 (190–390)	0.021
mMRC score median (IQR)	1 (1–3)	1 (1–3)	0.478
SGRQ total score	41±17	46±16	0.056
Symptoms	43±20	51±18	0.024
Activity	57±22	59±18	0.709
Impact	30±17	37±18	0.022

The Chi-squared test, Student's t-test, Welch's Approximation or Mann–Whitney U-test were used as appropriate. Data are presented as n (%), mean±SD and median (interquartile range), unless otherwise stated. P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{aO_2}: arterial oxygen saturation; mMRC: modified Medical Research Council; IQR: interquartile range; SGRQ: St George's Respiratory Questionnaire.

The above results indicate that BE-COPD may be classified as the benign version of COPD [37]. However, despite having a higher baseline FEV$_1$, BE-COPD patients show gas exchange abnormalities earlier, walk less and have a worse quality of life than smokers. In fact, after matching women with TE-COPD and women with BE-COPD according to age and severity of airflow obstruction, women exposed to biomass smoke persistently showed a lower quality of life and increased hypoxaemia [45]. Moreover, mortality is similar to that

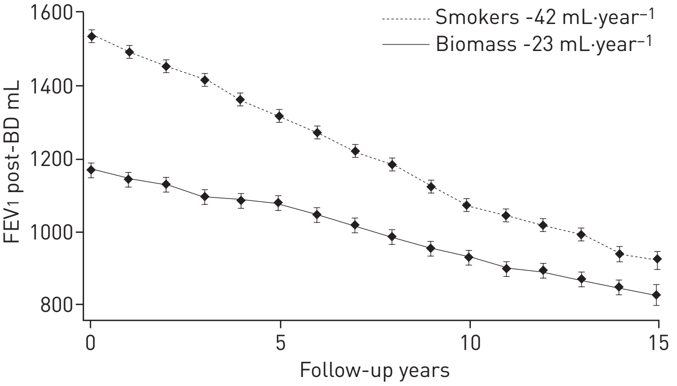

Figure 1. The rate of FEV$_1$ decline is significantly slower in patients whose COPD is caused by biomass. BD: bronchodilator. Reproduced and modified from [37] with permission from the publisher.

observed in smokers when data are adjusted according to FEV1 [39]. Therefore, BE-COPD is as harmful as TE-COPD.

Beyond lung function characteristics, there are a number of clinical contrasts between BE-COPD and TE-COPD, allowing two clearly separate COPD phenotypes to be demonstrated: 1) the chronic bronchitis phenotype for women with BE-COPD; and 2) the emphysema phenotype for smokers. In addition, due to the circumstances of exposure, women with BE-COPD tend to be older, shorter and have a higher BMI than those with TE-COPD [37, 40, 45]. BE-COPD presents clinically as a chronic obstructive disease with persistent cough, phlegm and dyspnoea [26, 31, 38, 40]. The majority of the reports seem to agree that bronchial symptoms are the most common clinical manifestations in these patients [31, 45].

Other histological and imaging evidence showing the predominance of airway diseases is found in necropsy and CT studies. Rivera *et al.* [46] found that lungs exposed to wood smoke demonstrated more severe bronchiolitis and less emphysema. *In vivo* assessment of COPD phenotypes is now possible with the advent of multidetector CT scanning. In a study by Camp *et al.* [45], female never-smokers with BE-COPD and females with TE-COPD were tested with completed CT at inspiration and expiration. Women in the tobacco group had significantly more emphysema, whereas in the BE-COPD group, air trapping predominated and the presence of cylindrical bronchiectasis was identified in 14% of patients. No bronchiectasis was found in those exposed to tobacco. Figure 2 presents a CT scan from a patient with BE-COPD and a CT scan from a patient with TE-COPD. Similar studies confirm the presence of an airway-predominant phenotype in these women [33].

Enhanced chronic inflammatory response

Both phenotypes of COPD, emphysema and chronic bronchitis are accompanied by an enhanced inflammatory response. Table 3 presents a summary of the most representative studies that involve biomarkers related to COPD pathogenesis [34–36, 47–49]. The manner in which BE-COPD is similar to TE-COPD in terms of inflammatory response is demonstrated

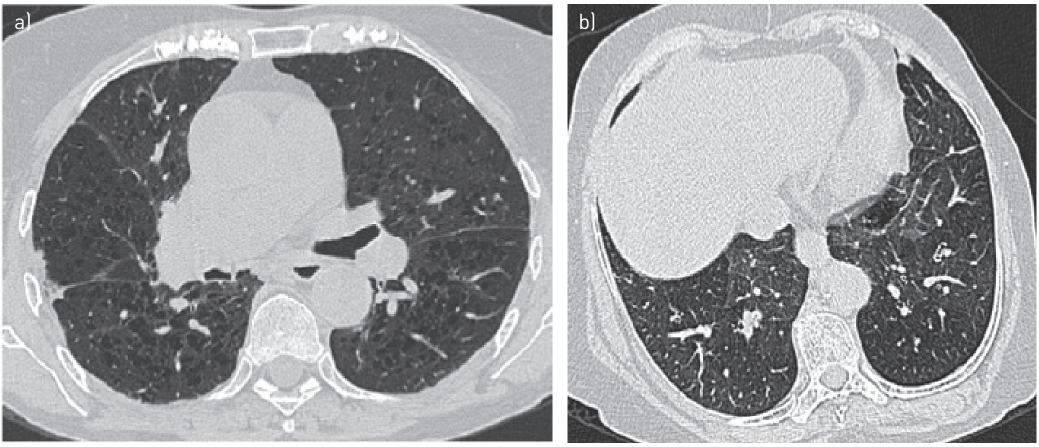

Figure 2. a) A CT scan from a woman with COPD caused by tobacco smoke. The CT shows severe centrilobular emphysema. b) A CT scan from a woman with COPD associated with biomass. The CT shows clear evidence of airway disease, including airway wall thickening, patchy areas of decreased attenuation, and vascularity suggestive of small airway diseases.

Table 3. Comparison of inflammatory biomarkers between subjects with COPD associated with biomass (BE-COPD), subjects with COPD caused by tobacco smoke (TE-COPD) and controls

First author [ref.]	Year	Inflammatory biomarker	BE-COPD sample	TE-COPD sample	Controls	Impact
Montaño [34]	2014	CRP ng·mL^{-1}	COPD biomass serum (n=40)	COPD tobacco smoke serum (n=40)	Serum from healthy women (n=40)	Systemic inflammation
			+++	+++	---	
Lahiri [35]	2007	Inflammatory sputum cells	Biomass users' wood smoke sputum (n=615)		LPG users sputum (n=282)	Inflammation and allergic reactions in the lungs
		Neutrophils, eosinophils, lymphocytes and macrophages	+++		+	
Montaño [36]	2010	Oxidative stress	COPD biomass serum (n=30)	COPD tobacco smoke serum (n=30)	Serum from healthy women (n=30)	Oxidative phenomenon associated with a reduction in FEV$_1$
		MDA, SOD	+++	+++	---	
Guzmán-Grenfell [47]	2011	Oxidative stress	COPD biomass plasma levels (n=27)	COPD tobacco smoke serum (n=31)	Serum from healthy women (n=15)	Alteration in NO metabolism
		Platelet arginase activity	+++	+++	----	
		Erythrocytes arginase activity	+++	---	---	
Banerjee [48]	2012	Pro-inflammatory cytokines and kitocine	Biomass users' wood smoke serum (n=142)		LPG cleaners' serum (n=126)	Neutrophilic inflammatory responses and oxidative stress
		IL-6, IL-12, TNF-α, IL-8, NO	++		---	
Banerjee [48]	2012	Expression of surface molecules by flow cytometry	Biomass users' wood smoke serum (n=142)		LPG cleaners' serum (n=126)	Neutrophilic inflammatory responses and oxidative stress
		CD16, CD35, CD11b, CD18	++		---	
Montaño [49]	2004	Macrophage elastolytic activity	COPD BAL (n=6)	COPD BAL (n=6)	Healthy BAL (n=3)	Increases MMP activity and expression
			+++	++	+	
Montaño [34]	2014	Elastolityc activity	COPD biomass plasma levels (n=40)	COPD tobacco plasma levels (n=40)	Serum from healthy women (n=40)	Systemic inflammatory phenomenon
		MMP-1, MMP-7, MMP-9 and MMP-9/TIMP-1	++	++	---	

+ to +++ indicate degree of severity from mild, moderate and severe, respectively. --- indicate within normal range. MDA: malondialdehyde; SOD: superoxide dismutase; NO: nitric oxide; LPG: liquefied petroleum gas; BAL: bronchoalveolar lavage; MMP: matrix metalloproteinases; TIMP: tissue inhibitor of metalloproteinase.

in clinical studies. Most of these studies are limited because of the small sample size, and they have not been replicated but, in general, they support the argument that many biomarkers currently identified as being involved in the pathogenesis of TE-COPD have also been described in BE-COPD. Such is the case of a cross-sectional study performed in an Indian population, which evaluated inflammatory cells in sputum of rural women who used biomass for domestic cooking. Subjects showed a significant increase in the number of alveolar macrophages and inflammatory cells in sputum. Neutrophils, eosinophils and lymphocytes in the sputum of biomass users were elevated in comparison with controls, suggesting infection, inflammation and allergic reactions in the lung [35]. Clinical studies carried out in women who cooked exclusively with biomass fuel suggest that there are alterations in immune defence. In a cross-sectional analysis that was conducted in a rural area of India, biomass users showed marked suppression in the total number of CD4+ and CD19+ cells, with an increase in the number of CD8+ T-cytotoxic cells and CD16+ and CD56+ natural killer cells. A consistent finding among biomass users was an increase in regulatory T-cells [50].

Other molecules involved in the pathogenesis of COPD due to tobacco have also been studied for biomass. Specifically, in comparison with healthy subjects, individuals with BE-COPD have increased levels of malondialdehyde and superoxide dismutase, which correlates inversely with FEV1 [34]. In addition, individuals exposed to tobacco and those exposed to biomass showed increased elastolytic activity of macrophages [49]. More recently, Montaño *et al.* [34] described an increase of several metalloproteinases and CRP. They found an inverse correlation between matrix metalloproteinase (MMP)-1, MMP-7, MMP-9, MMP-9/tissue inhibitor of metalloproteinase-1 and CRP plasma concentrations and FEV1, suggesting the presence of a systemic inflammatory phenomenon similar to that observed in COPD associated with tobacco smoking, which may also play a role in COPD pathogenesis. It has yet to be determined whether these mild or moderate differences in inflammatory responses are relevant and whether they explain the differences in the clinical and pathological presentations of COPD due to smoking or biomass, or whether the differences depend on susceptibility or the type and dose of smoke exposure.

Comorbidities

The last characteristic associated with the GOLD definition of COPD is the presence of comorbidities. Unfortunately, scarce information has been published on this topic. Golpe *et al.* [51], looking at comorbidities, compared a group of 122 BE-COPD subjects with 377 TE-COPD subjects, supporting the notion that comorbidities coexist in these group of patients. They found that the Charlson index >1 and the COTE index was similar in both groups. Similarly, they found that the proportion of subjects with other comorbidities, such as type 2 diabetes mellitus, ischaemic heart disease and anxiety, among others, was similar in both groups. These data support the notion that comorbidities coexist both in BE-COPD as in TE-COPD. Unpublished data from our clinic show that the prevalence of type 1 diabetes mellitus is higher in women exposed to biomass in comparison to women smokers (personal communication; A. Ramírez-Venegas). This finding may be associated with higher BMI and the trend for obesity observed in this population. This lack of information clearly demonstrates the need for additional research on this topic.

Cor pulmonale could be a comorbidity associated with biomass smoke exposure if we consider the fact that the abnormalities of small pulmonary arterioles [46] with intimal thickening may lead to pulmonary hypertension in individuals exposed to biomass smoke to a greater degree than in smokers [52, 53]. In a group of women exposed to wood smoke, researchers noted that the mean pulmonary artery pressure and total pulmonary vascular resistance were significantly higher than estimated in patients with tobacco-related COPD and ILDs [54]. Pulmonary hypertension and cor pulmonale may be leading causes of complications and death in BE-COPD.

Discussion

The case history presented at the beginning of this chapter describes a classic case in which a diagnosis of COPD in a nonsmoker has to be made. The patient has a history of chronic cough and respiratory symptoms, with imaging and the functional changes of COPD. By considering that this woman is not a smoker and has no history of occupational risk, the antecedent of biomass smoke exposure appears to be the only risk factor for developing COPD. However, the patient has not received the appropriate medical care for this diagnosis. She has experienced the adverse effects of her cultural, socioeconomic and environmental characteristics. In addition, the patient lacked medical awareness about the health consequences of her indoor air exposure. This patient represents one of the 30–75% of families using biomass fuel for cooking in rural areas of Latin America [6].

The patient studied here may have had a lower birth weight than the population average [20–23]. This and her history of acute lower respiratory airways infection are risk factors not only for lower lung function if the patient survives these respiratory health disadvantages, but also for developing COPD in adult life.

As an adolescent and as an adult she had chronic respiratory symptoms, which were largely ignored and, in general, she did not seek medical care due, in part, to the fact that her family believed that it was "normal" to have mild respiratory complaints and because she never received an appropriate medical diagnosis. Later in her life, she was diagnosed with a respiratory illness. In this particular case, she was advised that she had asthma due to her wheezing and received only bronchodilator treatment for several years. Therefore, there was a progressive increase in both dyspnoea and cough. In this sense, BE-COPD may be worse than the disease observed in smokers for two reasons: first, due to the adverse socioeconomic and environmental conditions; and second, because if under-diagnosis is an unresolved issue in COPD associated with tobacco smoking [55], it is clearly greater in biomass exposure [3]. Whether or not these women have ACOS requires further research. A recent study showed a greater proportion of mixed COPD–asthma phenotype in the biomass group than in the tobacco group [53, 56, 57]. However, evidence is inconclusive and additional information is needed.

Women with BE-COPD may have bronchiectasis [35]. However, the florid clinical picture of chronic cough with purulent mucus hypersecretion has not been observed. In fact, bronchiectasis was not observed on the CT scan of this patient.

Treatment at disease initiation is usually based on bronchodilators, as in this case. However, inhaled steroids must be added and eventually the combination of β_2-adrenergics, anticholinergics and inhaled steroids, along with supplemental oxygen, and the entire spectrum of treatment strategies recommended in the GOLD guidelines must be carried out [32]. However, no clinical trials are available to determine which intervention is best or whether the current GOLD recommendations are suitable for these women. Even with the existence of the recommendations, access to treatment is not always an option due to the social and economic conditions that accompany this disease.

Preventive measures are required to slow or stop the existence and progression of this entity. Only stoves burning cleaner fuel can improve the health of women in developing countries. Use of an improved biomass stove has reduced several adverse health outcomes, such as respiratory symptoms, sore eyes, headache and decline in FEV1 among women exposed to biomass, and may also eventually reduce COPD and its long-term consequences [58].

Conclusion

Patients with COPD exposed to biomass smoke are more likely to be women, with similar survival, molecular inflammation and comorbidities to subjects with TE-COPD. However, despite the similarities, these patients have less severe airflow obstruction and a slower FEV1 decline over time. Paradoxically, symptoms, quality of life, and gas exchange may be worse than in tobacco smokers.

Taking into account the three characteristics from the GOLD definition (airflow limitation, inflammation and comorbidities), we can conclude that women exposed to biomass share all of these characteristics and, therefore, have COPD. Additional research is necessary, in areas from epidemiology and pathogenesis to treatment and prevention.

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Chapter 4

α_1-antitrypsin deficiency

Damian Bruce-Hickman[1], Catherine M. Greene[2] and Bibek Gooptu[3,4,5]

Case history: Routine screening of a newly referred COPD patient reveals a low serum level of α_1-AT, and subsequent tests confirm that the patient is homozygous for the Z α_1-ATD allele. What is the current evidence for the use of α_1-AT augmentation therapy? What is the significance for family members and should they be screened for α_1-ATD? How would you explain why the disease can cause both lung and liver disease? What other diseases are linked with this condition?

Chapter summary: The emphysema of α_1-ATD is the best understood subphenotype of COPD in terms of its genetic basis, disease behaviour and major pathogenic mechanisms. However, this level of insight has not yet translated to a definitive cure, or even a tailored treatment that has proven robustly effective, for α_1-ATD. This apparent paradox drives controversy, by implying an urgent need to identify where knowledge is incomplete or existing data are misunderstood. From another perspective, it highlights how subphenotyping is a necessary element but is not sufficient for development of specific treatments to provide the best possible patient-centred care. In this review of ongoing debates in α_1-ATD we address, in turn, the involvement of different cell types, the extent of associated clinical phenotypes, the need to identify the optimal role of existing therapeutic options and how to develop new treatments. In doing so, we define important areas that are the subject of further active research, or that in our view require it.

Subphenotyping of COPD is viewed as an important approach for improved understanding of the natural history and personalised management of individuals affected by this pathological spectrum [1]. In general, robust definition of COPD subphenotypes is still at a relatively early stage [2], but α_1-ATD represents a longstanding example. It is, to date, the only clearly established genetic cause of COPD [3]. A mechanism whereby the genetic abnormality can result in lung pathology was identified many years ago [4, 5] and this is not contested. Even so, for α_1-ATD, subphenotyping defines a powerful context for understanding, but does not directly resolve, a wide range of questions regarding disease mechanisms and management in patients. Here, we aim to set out a general consensus and then articulate areas of live debate within the field.

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Current understanding of α_1-ATD

α_1-ATD was characterised just over 50 years ago as a syndrome of severe circulating deficiency of the dominant circulating antiprotease, α_1-AT, associated with emphysema [4, 6]. Typically, the lung disease was early-onset, bibasal and panacinar. Within a few years, further liver disease manifestations (neonatal hepatitis, hepatic cirrhosis and hepatocellular carcinoma) began to be identified [7]. Subsequently, associations with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis [8, 9], and panniculitis refractory to standard therapy have been established [10, 11].

α_1-ATD arises as a result of mutations in the *SERPINA1* gene [12] encoding α_1-AT, the key regulator of elastase activity in the lung [13, 14]. Well over 100 deficiency variants are now recognised. Some (Null variants) result in undetectable levels of circulating protein due to variant splicing, coding deletions and premature stop codons [15], but most are the result of missense mutations and are synthesised as full-length polypeptide chains. Mutants are conventionally defined by the electrophoretic phenotype of the variant α_1-AT on an isoelectric focusing (IEF) gel relative to the wild-type protein [16]. Wild-type is denoted “M” while mutants migrating faster and slower than the wild-type are denoted by letters that are, respectively, earlier and later in the alphabet. The α_1-AT status of individuals is described using the “proteinase inhibitor” (Pi) notation and may indicate the protein biochemical phenotype or the *SERPINA1* genotype. In practice, phenotyping cannot distinguish between the profile of a homozygote for an α_1-AT variant and a compound heterozygote for the same protein variant and a Null variant. Thus, individuals with a PiM profile on IEF are most likely to have a PiMM genotype, but could alternatively be PiMNull. As α_1-AT is expressed co-dominantly, it is useful to correlate phenotype with circulating levels of α_1-AT to confirm the likely status, with formal genotyping requested in discrepant or unclear situations. Homozygotes for the Z (Glu342Lys) variant are prone to the greatest burden of severe disease. This variant is found in populations of North European descent. It arose ~2000 years ago around Scandinavia and the Baltic coast [17], where its present day incidence is highest at approximately one out of 27 for heterozygotes (approximately one out of 2000 homozygote frequency) [18, 19]. A second common variant is the S (Glu264Val) allele that has its highest incidence in the Iberian Peninsula (peak heterozygote frequency one out of five) but is associated with far milder clinical consequences.

The Z mutation causes the polypeptide chain to misfold within the endoplasmic reticulum (ER) compartment of hepatocytes, which produce most of the body’s α_1-AT [20, 21]. The majority of the synthesised polypeptide undergoes degradation by quality control mechanisms for correct folding within the ER [22]. However, a proportion evades these mechanisms and self-associates to form polymers of noncovalently linked α_1-AT molecules that are retained within ER inclusion bodies. A small proportion of Z mutant α_1-AT is secreted into the circulation at levels typically ~15% of that of the M protein.

The clinical disease phenotype in PiZZ α_1-ATD results from a combination of deleterious gain- and loss-of-function effects of these events [23, 24] (figure 1). The intracellular misfolding and polymer build-up within the hepatocyte ER has toxic consequences that ultimately lead to liver disease. Milder disease mutants, such as the S variant, are less polymerogenic, and homozygote states are not associated with pathological accumulation of polymeric α_1-AT in hepatocytes, or liver disease.

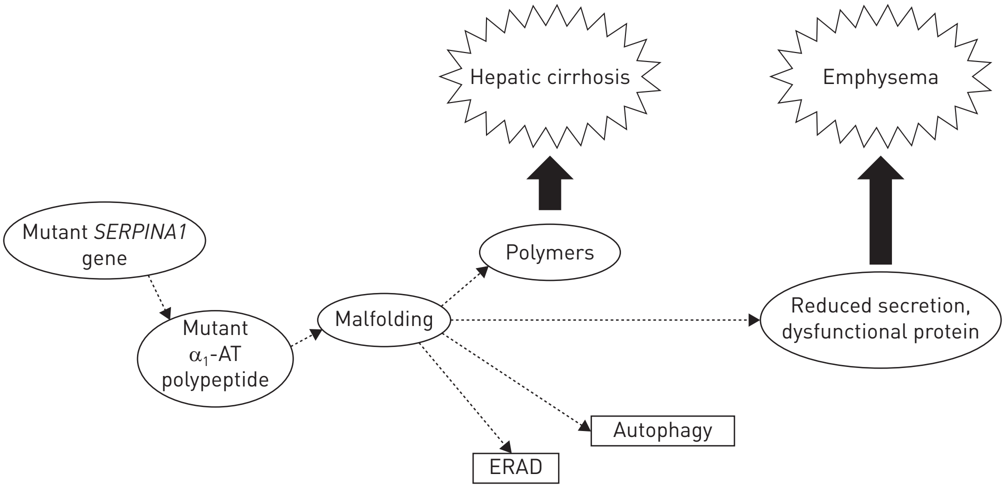

Figure 1. General understanding of how handling of the mutant protein product of the *SERPINA1* gene relates to liver and lung disease in α_1-ATD. ERAD: endoplasmic reticulum-associated protein degradation.

The critical function of α_1-AT is inhibition of human neutrophil elastase. In addition to the concomitant deficiency of circulating protein, the monomeric Z α_1-AT that is secreted is also less effective as an inhibitor of elastase than the M protein [25]. Therefore, in PiZZ individuals, during neutrophilic inflammation (*e.g.* in the context of smoking) lung tissue is vulnerable to elastase-mediated breakdown of elastin within the elastic fibres that are the major scaffold of lung parenchyma. In mammals, elastogenesis is a developmental process that peaks at birth and declines with age, so that it becomes unappreciable in adults [26]. α_1-ATD, therefore, predisposes to emphysema. To address this, augmentation (also known as replacement) therapy is a logical approach and is licensed for this use in many regions [27]. Overall, however, there remain many unmet clinical needs in α_1-ATD. Currently, they are only addressable by standard lifestyle advice and supportive measures for usual COPD and liver disease with organ transplant a consideration for end-stage disease. However, working to resolve ongoing questions regarding disease mechanism in α_1-ATD (figure 2) identifies novel therapeutic approaches (figure 3) [28, 29]. In the rest of this chapter we will, therefore, highlight areas of uncertainty and debate in terms of mechanistic pathways, current therapy and challenges faced in the development of a cure.

Disease mechanisms in α_1-ATD: live issues

How and when do deficiency mutants polymerise and how does the cell respond?

Two key questions about the mechanisms underlying α_1-ATD are currently contentious. They have implications for the development of specific therapies for α_1-ATD. First, what is the relationship between coexistent misfolding and polymerisation, *e.g.* when the common, severe Z deficiency allele is expressed? Secondly, does expression of polymerogenic mutants trigger the cellular stress responses to excessive misfolding?

Proteins fold to their native three-dimensional structure following, and possibly to some extent during, polypeptide synthesis (post- and co-translational folding). This is a complex and dynamic process that occurs very rapidly relative to the range of potential conformations

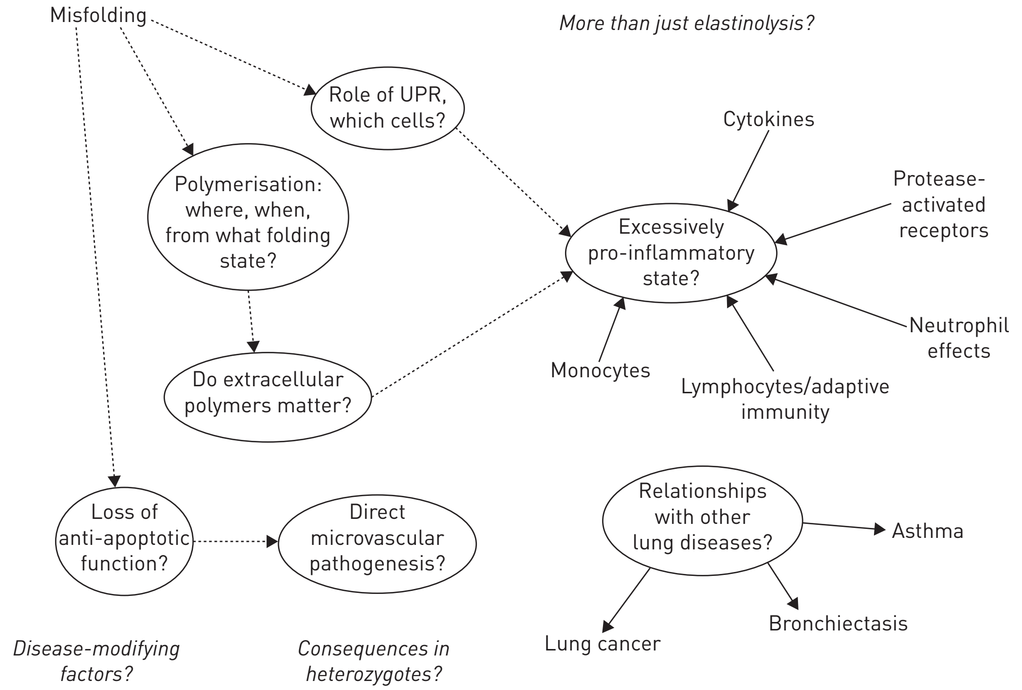
Misfolding
More than just elastinolysis?
Role of UPR, which cells?
Cytokines
Polymerisation: where, when, from what folding state?
Protease-activated receptors
Excessively pro-inflammatory state?
Neutrophil effects
Monocytes
Lymphocytes/adaptive immunity
Do extracellular polymers matter?
Relationships with other lung diseases?
Asthma
Loss of anti-apoptotic function?
Direct microvascular pathogenesis?
Bronchiectasis
Lung cancer
Disease-modifying factors?
Consequences in heterozygotes?

Figure 2. Overview of mechanistic questions and controversies in α_1-ATD. UPR: unfolded protein response.

available to the polypeptide chain: this is known as the Levinthal paradox [30]. Moreover, if aberrant structural states are populated these will usually have dysfunctional consequences. This situation has been addressed by the evolution of three related mechanisms that maintain homeostasis of protein folding (proteostasis) [31]. Some conformations accessible by protein sequences are energetically more favourable than others. Folding is, therefore, directed down free energy gradients through a so-called "energy landscape" with the native conformation of a globular protein usually representing the lowest free energy state. To complement this, a range of chaperone molecules interact with the polypeptide chain to favour conformations that are "on pathway" for adoption of the native fold [32]. The cell also possesses degradation machinery to prevent the persistence of aberrant structures [33].

All these processes are of particular relevance to α_1-ATD. The physiological native state is already unusual in representing a globular conformation that is trapped at a higher energy state than the global minimum in its folding landscape [34], a phenomenon known as metastability. Since chaperones normally prevent the population of such structures it is unclear how α_1-AT interacts with, or evades, ER-resident chaperone molecules to achieve this result. The most energetically stable state can be induced with purified protein in cell free *in vitro* conditions [35]. It is known as the latent conformation. Recent studies have suggested that the intracellular environment is inherently resistant to formation of latent α_1-AT even if it remains indefinitely in the ER folding compartment, or the chaperone capacity is modulated, or degradation is blocked [36]. The same applies whether the wild-type M or the more conformationally labile Z variant is expressed and under conditions where polymers are formed. The mechanisms behind this resistance to monomeric stabilisation in the intracellular environment, therefore, require further elucidation.

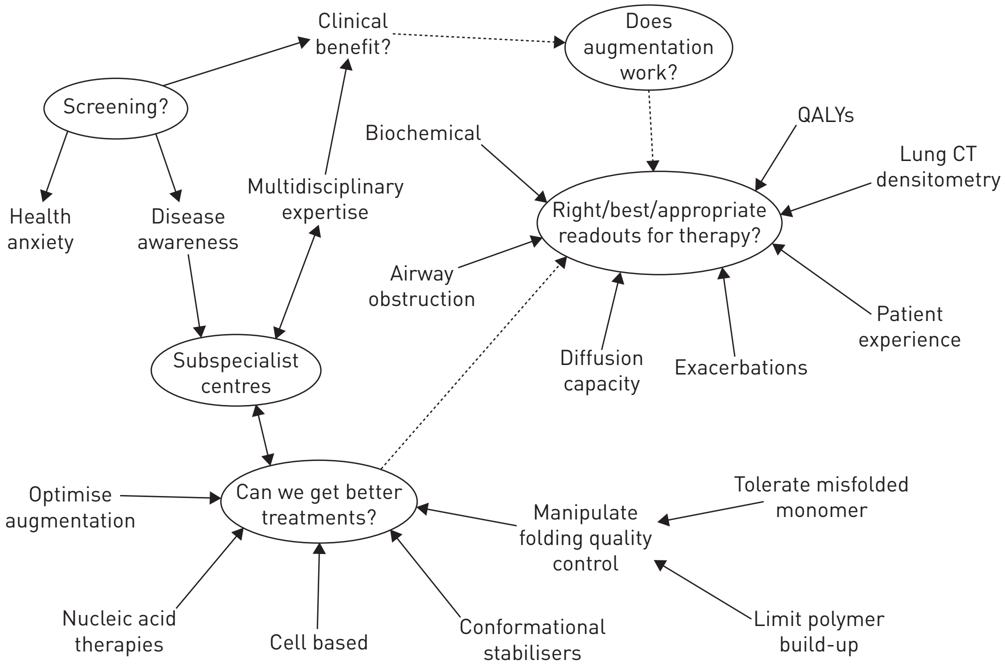
Clinical benefit?
Does augmentation work?
Screening?
Biochemical
QALYs
Lung CT densitometry
Multidisciplinary expertise
Health anxiety
Disease awareness
Right/best/appropriate readouts for therapy?
Airway obstruction
Patient experience
Subspecialist centres
Diffusion capacity
Exacerbations
Tolerate misfolded monomer
Optimise augmentation
Can we get better treatments?
Manipulate folding quality control
Nucleic acid therapies
Cell based
Conformational stabilisers
Limit polymer build-up

Figure 3. Overview of questions and controversies in α_1-ATD management and therapeutics.

In recent years the nature of the structural mechanism by which α_1-AT polymers assemble *in vivo* has become a focus of debate. *In vitro* studies demonstrate that α_1-AT has the potential to form stable polymers by three mutually exclusive linkage mechanisms (figure 4) [20, 37–44]. As yet, we do not know which types of polymers are most relevant to disease. Since characterisation of the underlying mechanism of α_1-ATD has been framed prominently in terms of understanding the structural behaviour of the protein, this has generated much contention. The structural details of the different models have been reviewed elsewhere, and may be of relevance to development of novel therapies specifically targeted to block the relevant linkage mechanism(s) [28, 45]. More broadly the debate relates to the question of when polymers form in terms of the protein folding process. Two mechanisms proceed *via* substantially unfolded intermediate species [43, 44], while the other arises from a near-native state [20, 38–40]. Pathophysiologically, the question can therefore be seen in terms of the relative contributions of polymers formed during folding *versus* those formed post-folding of the α_1-AT polypeptide chain to a native state. The former scenario envisages that misfolding leads directly to polymerisation through aberrant population of part-folded polymerogenic intermediates that may be on or off the normal folding pathway [43, 44, 46]. Post-folding, polymers may instead arise because of abnormal conformational behaviour of native α_1-AT in solution leading to population of a polymerogenic intermediate that may be more native-like [38, 47, 48].

On a related note, a number of studies have come to differing conclusions as to the cellular response to the expression, misfolding and polymerisation of deficiency variants of α_1-AT. Basal levels of protein misfolding within the ER are handled by the endoplasmic reticulum-associated degradation (ERAD) pathway, in which misfolded states are

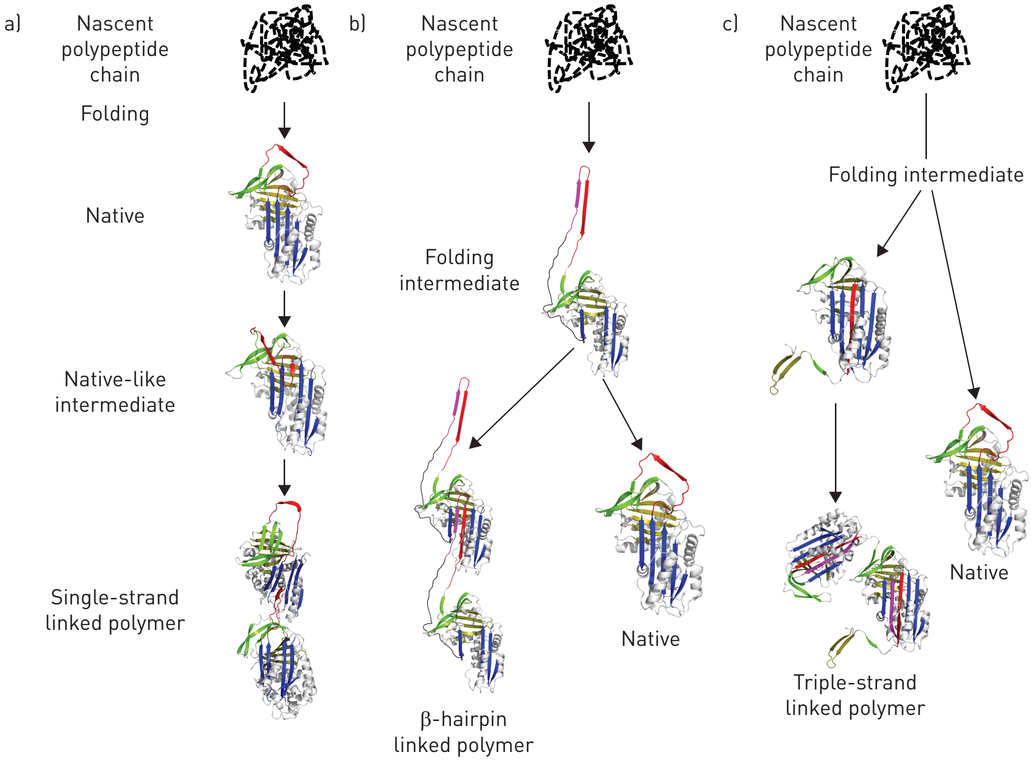
a)
Nascent polypeptide chain
Folding
Native
Native-like intermediate
Single-strand linked polymer
b)
Nascent polypeptide chain
Folding intermediate
β-hairpin linked polymer
Native
c)
Nascent polypeptide chain
Folding intermediate
Triple-strand linked polymer
Native

Figure 4. The three proposed mechanisms of α_1-AT polymerisation. The reactive loop/strand 4, β-sheet A is shown in red and β-sheet A in blue (strand 5, β-sheet A in magenta in β-hairpin and triple-strand linkage schemes), β-sheet B-related sequences are in yellow, and β-sheet C-related sequences in green. a) Single-strand linkage can occur post-folding to a native state ensemble, while b) β-hairpin linkage and c) triple-strand linkage will more likely arise from intermediate states that are far less folded.

recognised and retrotranslocated into the cytosol for ubiquitination and digestion by the proteasome [49]. If this is overloaded, the build-up of misfolded protein in the ER triggers the unfolded protein response (UPR) and ER stress [50]. These responses reduce net translation of proteins while selectively upregulating expression of ER chaperones to reduce the proteostatic load. However, persistent ER stress may lead to apoptosis. UPR activation is defined experimentally by activation of three response pathways reported by increased levels of phosphorylated elongation initiation factor 2α, activating transcription factor (ATF)4 and alternative splicing of X-box binding protein *(XBP)1* mRNA.

The $\text{Null}_{\text{HongKong}}$ variant of α_1-AT has a large C-terminal deletion due to a premature stop codon and so grossly misfolds without forming ordered polymers [51, 52]. This robustly triggers UPR and ER stress responses in cell models. However, studies assessing the cellular responses to misfolding and polymerisation of Z α_1-AT have generated apparently conflicting data regarding whether or not UPR and ER stress responses are activated. HIDVEGI *et al.* [53] found no evidence of UPR activation in PiZZ liver samples obtained *ex vivo*. Similarly, Chinese hamster ovary (CHO) cells expressing Z α_1-AT, that recapitulate the ER inclusion and low secretion phenotypes of hepatocytes in α_1-ATD liver disease, do not show the UPR and ER stress responses as assessed by highly sensitive reporters [54]. Instead polymers appear to trigger a calcium-dependent ER overload response to the build-up of ordered protein that leads to nuclear factor (NF)-κB signalling [55–57]. This also seems relevant to PiZZ hepatocytes *in vivo* [53]. ER stress was also not observed in PiZZ primary bronchial epithelial cells grown in culture [58]. In contrast, Carroll *et al.* [59] reported evidence for UPR activation in monocytes from individuals with α_1-ATD. The data indicated that Z α_1-AT accumulates intracellularly in ZZ monocytes and that the UPR is activated in quiescent ZZ compared with MM monocytes. ATF4 expression and *XBP1* splicing was increased in PiZZ monocytes, and expression of ER chaperone and ERAD genes were also higher.

Can both sets of findings regarding the UPR response to Z α_1-AT synthesis be correct? We propose a mechanistic framework that could reconcile the apparently divergent reports (figure 5). A general assumption may be that different cell lines may behave differently *in vitro*, with such behaviours sensitive to experimental conditions. Moreover, while the UPR and ER stress responses are important in their own right, to focus entirely on their presence or absence for a binary classification of cellular behaviour may obscure common events occurring upstream or in parallel. For example, even in PiZ(Z) cell lines that do not show UPR and ER stress responses, most of the mutant α_1-AT protein misfolds and is degraded rather than forming polymers. When synthesis of Z α_1-AT polypeptides is induced in CHO cells, ~70% of this material misfolds and is degraded by ERAD, while ~15% is retained within the ER in polymeric form [54, 57]. This leaves ~15% to be secreted, consistent with clinical findings *in vivo*. When the $\text{Null}_{\text{HongKong}}$ variant is expressed in the same system, the moderate increase in the quantity of misfolded α_1-AT (possibly exacerbated by the degree of misfolding per polypeptide) triggers the UPR and ER stress. This suggests that the difference in such response profiles in CHO cells expressing Z and $\text{Null}_{\text{HongKong}}$ α_1-AT variants relates to whether or not a threshold level of polypeptide misfolding is exceeded. This threshold presumably relates to the saturation of basal chaperone capacity and of ERAD mechanisms. Further support for this comes from the observation that PiZ CHO cells are more susceptible than PiM controls to the UPR and ER stress following a "second hit" proteostatic insult [57, 60]. The precise level of this triggering threshold may well be cell type specific, resulting in the UPR observed in PiZZ monocytes but not PiZZ hepatocytes. It is tempting to speculate that since hepatocytes are among the most prolific protein synthetic and secretory cells in the body, their tolerance of proteostatic challenge will be higher than other cells. Conversely, PiZZ cells that secrete far lower levels of protein (*e.g.* bronchial epithelial cells) will generate ER levels of misfolded α_1-AT that are orders of magnitude less and so do not exceed the threshold for UPR-triggering, even if it is set far lower [58].

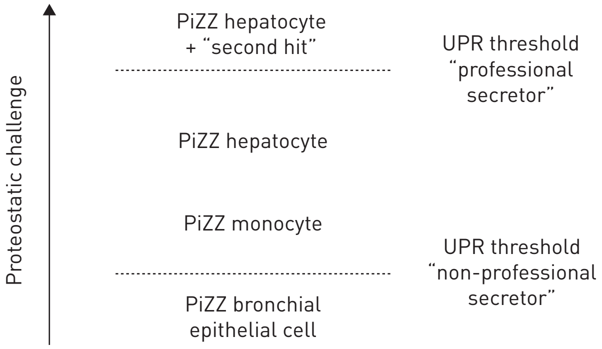
Proteostatic challenge
PiZZ hepatocyte + "second hit"
UPR threshold "professional secretor"
PiZZ hepatocyte
PiZZ monocyte
UPR threshold "non-professional secretor"
PiZZ bronchial epithelial cell

Figure 5. Model to reconcile discrepant findings for triggering of the unfolded protein response (UPR) and endoplasmic reticulum stress in different cell types.

Is the lung disease of α_1-ATD driven by more than just elastic tissue breakdown?

The protease–antiprotease balance model of lung parenchymal homeostasis is based on the assumption that uncontrolled elastase activity plays a dominant role in the pathogenesis of emphysema in α_1-ATD. This remains uncontentious and it is supported by data from small numbers of individuals identified with undetectable circulating levels of α_1-AT due to homozygosity for Null alleles of the *SERPINA1* gene [61]. These individuals had substantially more severe disease than PiZZ and PiSZ cases matched for age and smoking history [61]. The damaging consequences of dysregulated elastase activity on alveolar matrix integrity are obviously relatable to the emphysema phenotype in α_1-ATD. However, recent studies of structural changes in the small airways in emphysema pathogenesis indicated that loss of longitudinal elastic fibres may play an important early role [62, 63]. α_1-ATD might be expected to exaggerate this process and so the role of longitudinal fibre breakdown in the associated lung disease deserves specific investigation.

Elastase has a wider role in lung inflammation than acting solely as an executor of elastin breakdown in the extracellular matrix. Its dysregulation, therefore, has multiple parallel pro-inflammatory implications relevant to the lung disease of α_1-ATD. Excess elastase cleaves protease inhibitors further exacerbating the protease imbalance. It can also activate cell surface receptors causing signalling cascades that lead to upregulation of cytokine and mucin production, or that activate or induce the expression of additional proteases [64, 65]. For example, elastase can induce MUC5AC mucin expression in airway epithelial cells. The process involves dual oxidase (Duox)1, (a) dismutase and (a) metalloprotease (ADAM)-17 and epithelial growth factor receptor (EGFR) [66, 67]. In contrast, elastase may also mediate some immunomodulatory effects [68]. This could affect therapeutic strategies based around the development of direct elastase inhibitors [69]. While free elastase appears to have a predominantly pro-inflammatory effect overall, the relative importance of these non-elastinolytic effects relative to matrix degradation remain to be elicited *in vivo*.

In addition to inhibiting elastase, α_1-AT is an effective inhibitor of other serine proteases, such as another neutrophil-derived enzyme, proteinase 3, and has been implicated in cross-class inhibition of caspase [70] and metalloprotease [71] enzymes. Furthermore, a number of reported effects of native α_1-AT on immune modulation and promotion of matrix integrity [72], and pro-inflammatory consequences of α_1-ATD are, as yet, not clearly relatable to antiprotease functions. Indeed, at least some immunomodulatory actions of native α_1-AT appear independent of its antiprotease activity [73–75]. Such broader biological activities can be rationalised in terms of disease mechanisms, but the extent of their importance *in vivo* largely remains to be ascertained.

Does it matter where the α_1-AT found in the lung is made? The liver synthesises a large quantity (1–2 g) of α_1-AT daily, and in PiMM individuals it circulates at $\sim$1.5–3.5 $\mathrm{g \cdot L^{-1}}$ ($\sim$30–70 $\mathrm{\mu mol \cdot L^{-1}}$). In the presence of acute inflammation, hepatic production and circulating levels increase up to five-fold. Most of the α_1-AT in the lung is derived from the circulating protein that enters the lung by passive diffusion. However, local production of α_1-AT within the lung is increasingly recognised, albeit at much lower levels than from hepatocytes. α_1-AT is synthesised by type II alveolar epithelial and bronchial epithelial cells [76–78] and by immune cells found in the lung: neutrophils, monocytes and alveolar macrophages [79–83]. The proportion of total lung α_1-AT derived from such cells is probably very low relative to that derived from hepatic production. This raises the attractive possibility that boosting the concentration of α_1-AT in the immediate vicinity of such cells may play specific roles in lung microenvironments. In particular, this may be relevant to inflammatory and immune responses. Inflammatory stimulation of monocytes by lipopolysaccharide (LPS), IL-1β or TNF-α is associated with increased production of α_1-AT by monocytes [84]. Similarly, the co-packaging of serine proteases with α_1-AT in the azurophilic granules of neutrophils has been described, and so might provide local protection for those cells from potential harm when elastase is released [79, 85]. In addition, locally produced α_1-AT could modulate innate and adaptive immune responses [86–88] through short-range (autocrine/paracrine) effects. While the *in vitro* studies detailed below provide data consistent with such mechanisms, their *in vivo* importance remains unsettled. Determining this may well require a combination of co-culture experiments and characterisation of *ex vivo* material in health and deficiency states.

Cytokine changes

Elastase is found in close spatial and temporal relationships with inflammatory cytokines [89]. This probably relates to its ability to liberate cytokines from storage in the extracellular matrix and on cell surfaces, and play a role in their activation from pro-cytokines [90]. Moreover, elastase is implicated in the release of the pleiotropic cytokine transforming growth factor (TGF)-β in its latent form from stores in the extracellular matrix [91]. Excessive elastase activity may therefore increase TGF-β availability. α_1-AT may also have a significant impact on reducing the inflammatory profile of cytokines produced in response to stimuli [92]. Dilution-induced stimulation of cells in whole blood from α_1-AT deficient patients significantly increased IL-8, TNF-α, IL-1β and IL-1 receptor antagonist (IL-1Ra) relative to controls. Addition of exogenous α_1-AT significantly attenuated the production of the pro-inflammatory cytokines IL-8, IL-6, TNF-α and IL-1β, but not the anti-inflammatory cytokines IL-10 and IL-1Ra.

Secretion of pro-inflammatory IL-8 is increased from primary bronchial epithelial cells derived from PiZZ patients relative to controls [58]. This is mediated by increased protease activity of the membrane-bound ADAM family member, ADAM-17, that can liberate EGFR ligands. Signal transduction results in extracellular signal-regulated kinase 1/2 phosphorylation and excess nuclear factor (NF)-κB signalling to activate pro-inflammatory pathways. This response is abrogated by administration of M α_1-AT. Since ADAM-17 has recently been identified as a cross-class protease target of α_1-AT [71], regulation of this pathway may be an important autocrine/paracrine function of α_1-AT secretion by airway epithelial cells *in vivo*.

Cytokine secretion responses to α_1-AT may vary over time to mediate a biphasic immunomodulatory response. In lung endothelial cells, α_1-AT administration causes an initial increase in TNF-α signalling, while prolonged exposure reduces this [93]. Data from studies in mouse and man have been interpreted to support similarly biphasic responses over time to α_1-AT in LPS (endotoxin)-induced airway inflammation [88, 94].

Signalling via protease-activated receptors

Protease-activated receptors (PAR1–4) are a family of cell surface G-protein coupled receptors with important roles in mediating inflammatory and fibrotic changes in response to tissue injury [95]. PAR1 and PAR2 are expressed on lung epithelial, fibroblast and endothelial cells, and alveolar macrophages. PARs 1–4 are also found on cells recruited to the lung during innate responses to damage: neutrophils, monocytes and platelets. PARs are activated or modulated by the action of serine proteases upon an N-terminal motif that can then participate in conformational change leading to signal transduction with potential anti- or pro-inflammatory outputs. Classically serine proteases of the coagulation pathway are implicated. α_1-AT has potential for relatively modest inhibition of such enzymes [96–98]. However, its target enzymes elastase and proteinase 3 participate in complex activating and/or modulating interactions with PARs 1 and 2 [99–104]. Moreover, it inhibits the cell surface bound protease, matriptase, that appears to be a physiologically relevant activator of PAR2 with which it co-localises, *via* a slow but tight interaction [105, 106]. The degree to which local or more diffuse dysregulation of these serine protease–PAR interactions impacts upon lung inflammation and tissue responses in α_1-ATD is, as yet, under-explored.

Neutrophilic inflammation

α_1-ATD has been particularly associated with excessive neutrophilic inflammation in the lung [107–112], although not all studies have clearly supported this [113, 114]. Moreover, there is a significant correlation between the initial neutrophil elastase burden in these α_1-AT deficient individuals with mild lung function impairment and the subsequent decline in FEV1 [112]. The transfer of neutrophils across endothelial barriers is generally believed to be dependent on proteases, and serine proteases in particular [115]. Elastase is implicated, as is proteinase 3 [116, 117], and addition of α_1-AT interferes with neutrophil transfer across an endothelial cell barrier [118]. By contrast, neutrophils increase production of α_1-AT upon migration into tissues [119], supporting a need for local control of protease activity.

A central role for elastase in mediating neutrophil migration is challenged by findings that administration of α_1-AT causes equivalent reductions in neutrophil infiltration into the lung and adhesion in wild-type and elastase knockout mice following LPS challenge [73]. This could be rationalised in terms of more important roles for proteinase 3 or even protease-independent pathways that may be regulated by α_1-AT [74]. It also may reflect the *in vivo* significance of ADAM-17-mediated pro-inflammatory signalling [58, 71]. In addition to involvement in NF-κB activation and IL-8 secretion as defined in bronchial epithelial cell cultures, ADAM-17 (also known as TNF-α converting enzyme (TACE)) activates TNF-α by cleavage of its precursor protein. Moreover, it can cleave an immunoglobulin receptor (FcγRIIIb) from its glycophosphatidylinositol-anchoring to the neutrophil membrane. It does so following binding of a soluble immune complex to FcγRIIIb. The liberated ternary antigen:immunoglobulin:FcγRIIIb complex can mediate chemotaxis. α_1-AT also appears to act to reduce chemotaxis by binding to IL-8. This prevents the interaction of IL-8 with its neutrophil bound receptor CXCR-1 and hence downstream pathways leading to cytoskeletal reorganisation and chemotaxis.

As well as controlling neutrophil migration, α_1-AT may play some role in the magnitude of damage effected by these cells. α_1-AT derived from human serum can diminish or halt superoxide release from human neutrophils in response to stimuli in a dose-dependent manner [120]. This is consistent with data from studies using other serine protease inhibitors, suggesting that this relates to its antiprotease activity [121]. Pre-treatment of neutrophils with synthetic serine protease inhibitors reduced the superoxide release of these cells in response to TNF-α. The amount of superoxide released by neutrophils is related to the concentration of α_1-AT to which they are exposed. Moreover, reactive oxygen species (ROS) production and degranulation is increased in neutrophils in α_1-AT deficient patients [122]. Neutrophils from these PiZZ patients demonstrate increased membrane TNF-α levels and release more granules, and also produce ROS more rapidly. α_1-AT augmentation rescues this phenotype, supporting a loss-of-function mechanism in disease. α_1-AT associated with the neutrophilic cell surface TNF-α receptors (TNFR1 and 2) and reduced their complexation with TNF-α. A small study demonstrated greatly increased levels of pro-inflammatory human neutrophil peptides in bronchoalveolar lavage (BAL) fluid from PiZZ individuals relative to healthy controls [123]. Inflammatory effects of these peptides were abrogated by α_1-AT treatment *in vitro*.

α_1-AT deficient alveolar macrophages spontaneously release around threefold more neutrophil chemoattractant activity than PiMM alveolar macrophages [107]. One measure of this activity is leukotriene (LT)B4, which is increased in the lung in α_1-ATD. Moreover, the binding of free neutrophil elastase stimulates further release of LTB4. Release of elastase by neutrophils into the lung interstitium sets up a pro-inflammatory positive feedback loop since the degradation products of elastin are themselves chemotactic for neutrophils, monocytes and alveolar macrophages [124]. Similarly *in vivo*, excess free airway elastase cleaves the cell surface molecule CXCR-1 from neutrophils to generate a soluble fragment that is chemotactic [125]. This action simultaneously modulates IL-8 signalling to increase neutrophil activation and degranulation, although it also impairs bacterial killing capacity. These studies demonstrated the significance of their mechanistic findings in disease states *in vivo*: effect sizes increased by disease type as the concentration of airway free elastase increased. Thus, these effects were much more prominent in CF than in usual COPD. No α_1-AT deficient individuals were included in these studies. However, the potential relevance of these findings in this condition was underscored by the observation that administration of inhaled α_1-AT restored the bacterial killing phenotype to neutrophils [125, 126].

Neutrophils are now known to kill pathogens by neutrophil extracellular traps (NETs) to complement their roles in phagocytosis and toxic release of protease and reactive oxidant species [127]. NETs are complexes of DNA and antimicrobial proteins, and are vital components our innate immune system [128]. NETs are complex structures tailored towards the size and type of pathogenic organism [129]. The formation of NETs is predominantly initiated by ROS production, but "NETosis" is also dependent on other contributions, including from neutrophil elastase. Undoubtedly, NETs are a key component of the immune system, and are conserved across species; however, they may also be problematic in chronic inflammatory disease. For example, NETs are important contributors to the tenacious qualities of mucus in the lungs of CF patients [130]. The histone component of NETs has been implicated in cytotoxicity against alveolar epithelial cells, suggesting that NETs may cause tissue destruction [131]. High total lung DNA levels, interpreted as a surrogate for NET concentration, have been found to correlate with obstruction, suggesting that NET formation may impact on lung decline [132]. In usual COPD, exacerbations are associated with significant NETosis. α_1-AT augmentation therapy may impact on the structure of NETs [133]. Morphologically, NETs from α_1-AT augmented patients are significantly different compared with those produced by neutrophils from non-deficient patients. The mechanism by which this arises, and the contribution of NETs to pathogenesis of lung disease in α_1-ATD, remains to be elucidated.

α_1-AT also prolongs neutrophil lifespan [134]. This may be related to the ability of α_1-AT to inhibit Calpain-I, a known mediator of neutrophil apoptosis, or through blockade of TNF-α activation by ADAM17 inhibition. Neutrophils from PiZZ α_1-AT deficient patients have double the rate of apoptosis of healthy controls [135]; this is associated with ER retention of Z α_1-AT and evidence of an ER stress response.

Monocytes

PiZZ monocytes express significantly higher cell surface levels of CD14 receptors, which are responsible for detection of bacterial LPS on monocytes, than PiMM monocytes [136]. Moreover, when stimulated with LPS they also produce higher levels of IL-6, IL-8, IL-10, chemokine (C-X-C motif) ligand (CXCL)1 and macrophage inflammatory protein 1α than PiMM cells [59]. These effects are associated with NF-κB activation *via* protein kinase B as well as evidence of UPR activation. Conversely, incubation of monocytes with α_1-AT is associated with increased production of the anti-inflammatory IL-1ra [137]. The effects of α_1-AT on the monocyte inflammatory repertoire may be biphasic with respect to time [138] and concentration [139]. Early exposure and lower concentrations may augment the initial acute phase response while longer duration and higher concentrations counter the potential for excessive or chronic inflammatory states. Interestingly, in monocytes neither the monomeric state of α_1-AT nor its activity [93] appears to be important for these effects. The degree to which PiZZ monocytes and alveolar macrophages are rendered more inflammatory by gain-of-function as well as loss-of-function mechanisms, and the importance of this monocyte phenotype *in vivo* remains to be ascertained.

Lymphocytes and adaptive immunity

Adaptive as well as innate immunity is recognised to play a role in the pathogenesis of usual COPD. A strong signal for this comes from the prominence of lymphocytic infiltration into airway tissue in COPD [140], with a predominant $CD8^+$ T-lymphocyte phenotype. Moreover within the small airways, lymphocytic organisation into lymphoid follicles correlates with disease severity [141]. How far this association relates to an ameliorative response and/or to maladaptive effects of the follicles remains to be clarified. So too does the mechanism by which smoking generates antigenic triggers for this reaction; microbiome changes and elastin degradation products have been proposed within pathogen-induced [142] and autoimmune [143] models.

In vitro and *in vivo* studies of mouse models demonstrate that α_1-AT exposure increases population of immunoregulatory, tolerogenic phenotypes in T-lymphocytes (T_{reg}) [144], dendritic cells [145] and B-lymphocytes [146]. In leukaemia patients who had received haematopoietic stem cell allografts such responses were coupled with an increase in a natural killer (NK) cell $NK1.1^+$ phenotype [147]. This combination improved specificity of the immune response (graft-*versus*-leukaemia response favoured over graft-*versus*-host disease). Such observations raise the question of whether dysregulation of adaptive immunity contributes to the more aggressive progression of COPD pathomechanisms in α_1-ATD. Despite the attractiveness of this hypothesis, direct evidence supporting its relevance *in vivo* remains scanty. A small study of anti-elastin autoantibody levels in BAL in COPD and PiZZ α_1-AT deficient individuals with normal spirometry showed similar, nonsignificant increases in both these subject groups relative to unmatched controls [143]. While the PiZZ group had a younger mean age (41.6±19.8 years) than the COPD group (67.1±8.9 years), this group was characterised by near-normal FEV_1 characteristics. The pathophysiological significance of these findings for α_1-ATD relative to usual COPD is therefore unclear. Recent histopathological studies of explanted lungs with end-stage emphysema confirmed the presence of similarly increased $CD8^+$ and $CD4^+$ T-cells, and B-cells with predominant mono-/oligo-clonality in α_1-ATD and usual COPD [114]. The correlation between lymphoid follicles and disease severity was also similar between these two groups as was upregulation of the cytokine IL-32 that plays a role in inducing autoimmunity. Interestingly, in addition to a slightly younger age at transplant (53±3 *versus* 57±1 years), the clearest difference between the subject groups was in the number of lymphoid follicles observed. These were significantly increased in α_1-AT deficient emphysema even relative to the elevated numbers seen in usual COPD-related end-stage disease ($p=0.009$). This supports the mechanistic relevance of data showing a role for α_1-AT in airway immunomodulation *in vivo* and so opens the way for further characterisation of immune dysregulation in α_1-ATD.

How important is increased cellular apoptosis in α_1-ATD?

Within the lung, increased apoptosis of epithelial cells, *e.g.* in oxidative stress conditions appears to be of relevance to COPD pathogenesis [148, 149]. A number of studies support a role for α_1-AT in the prevention of cellular apoptosis in bronchial [150] and alveolar epithelial cells [151], endothelial cells [152], and neutrophils. Similar findings in experiments with pancreatic islet β-cell lines are being explored as a means of improving survival of transplanted islet cells [153].

Native α_1-AT has a pro-survival effect on lung alveolar epithelial and endothelial cells [151, 154]. It is internalised by the cells of interest, and has been reported to prevent caspase-3 activation. This effect appears specific to the native, active conformer of α_1-AT and may involve cross-class inhibition of cysteine proteases. Overexpression or intravenous augmentation of α_1-AT significantly reduced alveolar wall destruction driven by apoptotic mechanisms downstream from vascular endothelial growth factor blockade. Human spirometry studies show that KCO may progressively decline in the face of preserved FEV1 in α_1-AT deficient patients [155], consistent with a vascular pathology. The mechanics of this protective response in α_1-AT augmentation are controversial and require further investigation. Complex mechanisms for the cellular uptake of α_1-AT and its subsequent intra- and transcellular trafficking are being elucidated in lung endothelial cell models [152, 156]. Even so it remains unclear how α_1-AT can inhibit cytoplasmic pro-apoptotic pathways following synthesis or uptake, since it is translated into the ER, while endocytosis should result in its containment in intracellular vesicles.

Do extracellular polymers matter?

In vivo, extracellular polymers of α_1-AT are found in the circulation and organs of PiZZ individuals [157]. In the lung they have been demonstrated in BAL [158] and in the interstitium [109]. Polymers have been found in the microvasculature of a PiZZ individual with vasculitis [159] and in the skin of PiZZ patients with panniculitis [160]. They have even been found in the BAL of a patient following liver transplant for PiZZ α_1-ATD-related liver disease, suggesting that local production of Z α_1-AT results in lung polymers [161]. α_1-AT polymers are also found in preparations of augmentation therapy, together with the latent conformer [36, 162].

It is therefore, as yet, unknown to what extent extracellular polymers of α_1-AT resemble those sequestered within the ER, or even each other, in terms of their protein structural organisation. Given the data supporting the differences in structural morphology between polymers formed in different experimental conditions *in vitro* [37, 39, 41, 43, 44], it is possible that different environments *in vivo* favour formation of structurally distinct polymer species. On a related note, we do not know the proportions of extracellular polymers that assemble intracellularly and are then secreted, compared with polymers formed from secreted monomeric material. Circulating polymers, like those observed in the supernatant of cell culture models of disease, differ from those retained intracellularly by having similarly mature glycan chains to secreted monomer [20, 57]. However, this does not prove that all, or indeed any, of them are derived from secreted monomeric material that polymerises outside the cell. Trafficking of preformed polymers along the secretory pathway could be accompanied by generally similar trimming of sugar chains to that undergone by secreted monomer.

The extent to which extracellular polymers are of biological importance through gain-of-function, rather than loss-of-function, remains to be clearly established. Pro-inflammatory gain-of-function within the lung is suggested by studies *in vitro*, in mouse models and in lung explants from patients with end-stage α_1-ATD-associated emphysema associated with usual COPD or emphysema. These indicate that polymers are chemotactic for neutrophils, adhere to them, activate them and will cause their degranulation in the interstitium where polymers and neutrophils co-localise [109, 163]. This combination of effects could explain the pattern of aggressive panlobular emphysema seen in α_1-ATD [24]. However, not all studies have supported the ability of polymers to activate neutrophils [164]. Moreover in a small study, patients homozygous for Null mutations had worse lung function than a combined population of PiSZ and PiZZ individuals matched for age and smoking [61]. This was interpreted as indicating that the increased loss of function in the Null homozygotes relative to PiSZ and PiZZ groups might be more deleterious than any gain-of-function effects in the Z allele carriers *e.g.* due to polymer burden. However, these findings are far from conclusive due to the understandably small numbers of Null homozygotes and the pooling of the “non-Null” (PiSZ and PiZZ) groups for the comparisons. A more thorough understanding would be gained if the relative proportions of native and polymeric α_1-AT in the circulation and within the lungs could be assessed in PiZZ individuals with emphysema. The degree to which the absolute values of native and polymeric α_1-AT and the ratio of the two states could then be correlated with disease severity, inflammatory status and progression could then be compared. The development of conformer-specific antibodies for polymeric and different monomeric states suggests that such studies may become feasible in future [36, 157, 159, 165, 166].

The presence of α_1-AT polymers in tissue associated with excessive neutrophilic inflammatory damage in PiZZ anti-proteinase 3 ANCA-associated vasculitis [159] and panniculitis [160] supports a biological role for extracellular polymers in disease. The reported benefits of α_1-AT augmentation in both of these disease manifestations [160, 167–169] could arise through blockade of elastase over activity, which will tend to result from either gain- or loss-of-function mechanisms. Such therapeutic effects therefore do not exclude gain-of-function drivers of pathology.

What are the important modifiers of genotype–phenotype correlation in α_1-ATD?

α_1-ATD is viewed as a monogenic disorder. However, it displays variable penetrance even when exposure to clear environmental triggers of disease, such as cigarette and alcohol consumption for lung and liver disease, respectively, are appropriately weighted [170, 171]. This variation is observed even amongst first degree relatives with the same genotype. It therefore seems certain that genetic modifiers exist in α_1-ATD. However, the nature of these modifiers remains to be clarified, with most of the observed modification as yet unaccounted for. For liver disease, a single nucleotide polymorphism in a gene encoding the ERAD pathway protein ER mannosidase I appears to mitigate severity [172]. For lung disease, polymorphisms in iron responsive element binding 2 and the neuronal acetylcholine receptor subunit $\alpha3$ that may relate to nicotine addiction potential have been associated with airflow obstruction [173]. So too has a polymorphism in the promoter region of the gene encoding the immunoregulatory cytokine IL-10 [174]. The polymorphism is associated with lower IL-10 levels, suggesting that loss of the immunomodulatory roles of α_1-AT may have relevance to the lung disease of α_1-ATD.

Clinical implications for heterozygotes: what is the true scale of the risk?

The concept of α_1-ATD as an autosomal recessive disorder has been challenged by recent studies. The major disease associations of the PiZZ state are well established. However, α_1-AT expression is co-dominant. This is important because individuals who are heterozygous for the Z allele therefore have intermediate levels of α_1-AT compared with MM or ZZ homozygotes. Until recently the concept of a threshold circulating α_1-AT level (11 μM) that conferred adequate protection to confer no increased risk of lung disease above that in PiMM individuals was widely accepted. This value was related to levels seen in SZ heterozygotes, who were believed to be at low increased risk of COPD.

Nevertheless, various studies have attempted to address the question of whether MZ heterozygosity is a risk factor for COPD and a meta-analysis of these studies from 2004 estimated an increased risk of COPD in MZ *versus* MM individuals with a combined odds ratio of 2.31 [175]. Although the case control studies therein showed an increased odds ratio for COPD, this was not confirmed in cross-sectional studies. However, collectively these studies had a number of methodological and design flaws such as small sample sizes, selection bias and inadequate control for cigarette smoke exposure. Molloy *et al.* [176], therefore, recently undertook a family based study using a study design that lacked ascertainment bias and used a fastidious methodological approach to determine the true risk of COPD in MZ heterozygotes. In their study 99 MM and 89 MZ non-index subjects were selected from 51 MZ probands with COPD. There was no difference in lung function in never-smoking MM *versus* MZ individuals. However, MZ individuals who smoked had an odds ratio for COPD of 10.65. These results are made all the more convincing compared with previous studies in that the data was derived from a genetically homogenous population in which COPD was diagnosed using standardised criteria, and appropriate covariate analysis was used to control for age, sex and cigarette smoke exposure. Thus, these findings have important consequences for global lung health given that there are estimated to be 116 million carriers of α_1-ATD alleles worldwide, principally the Z and S alleles, with approximately 7 million MZ individuals predicted to be in the USA and 10 million in Europe [177, 178]. Identifying and managing the health of MZ individuals, principally through education and smoking cessation programmes, could postpone or even prevent the development of lung disease in these individuals and would ultimately decrease the global healthcare burden of COPD.

These data also support the relevance of protease–antiprotease imbalance in the pathogenesis of COPD beyond the PiZZ state and are consistent with pro-inflammatory lung polymers of Z α_1-AT playing a role in pathogenesis in PiMZ individuals. The oxidative effects of cigarette smoke exposure inactivate α_1-AT as an inhibitor of elastase [179]. In addition, they are reported to induce α_1-AT polymerisation in the lungs of transgenic PiZ but not PiM mice [180] with an associated increase in neutrophil influx. This suggests that inflammation could be enhanced in PiMZ smokers by intrapulmonary polymerisation. Whether there are inflammatory consequences in the lungs of MZ or other Z heterozygotes in the absence of cigarette smoke exposure is not fully known. However, excessive pulmonary neutrophilia and elevated airway IL-8 levels are observed in never-smoking PiMZ individuals with normal spirometry [181]. The presence of intrapulmonary polymers, and therefore, an exaggerated inflammatory response, in PiMZ individuals has even been proposed to provide an antimicrobial survival advantage [182]. This could explain the Z allele's persistence in Northern European populations prone to lung infections in the pre-antibiotic, pre-cigarette era. Once again, a correlation between the levels of polymers and functional monomeric protein *in vivo* and measures of lung inflammation would be invaluable in dissecting loss-of-function from gain-of-function contributions to these observations.

PiMZ heterozygotes do show accumulation of α_1-AT in hepatocyte ER inclusions, but to a lesser extent than is observed in PiZZ individuals. The risk of liver disease in PiMZ heterozygotes remains uncertain. A recent retrospective, single-centre study of 1036 patients assessed for liver transplantation because of severe disease found evidence of much higher PiMZ carrier frequencies than in the general European population (2.8%) [183]. This was particularly the case in subgroups with non-alcoholic steatohepatosis (17.7%) and alcohol-related (9.9%) aetiologies ($p<0.0001$), with underrepresentation of PiMZ individuals in biliary cirrhosis ($p<0.004$). These observations require validation in prospective studies of populations from other centres before their relevance to PiMZ individuals can be truly ascertained. However, they suggest that, as in the lung, disease-modifying factors should be aggressively pursued.

For compound heterozygotes of two different deficiency alleles (most commonly PiSZ), the risk of COPD is predicted to relate to circulating α_1-AT levels. However, this does not address whether the circulating protein is in the active, native conformation. If it is not then the levels of total α_1-AT will underestimate the degree of functional deficiency. The liver disease risk in α_1-ATD appears to correlate well with intracellular polymer accumulation. Clinical predictions can therefore be made where polymerisation potential of the two variants has been assessed, particularly if this includes assessment of their potential for heteropolymerisation [38, 184]. However, *in vivo* data to confirm the degree to which these predictions hold true are lacking, even for PiSZ individuals.

Does suboptimal α_1-AT status predispose to other lung diseases?

Asthma

Anecdotally, many patients with α_1-ATD report "misdiagnosis" with asthma prior to the identification of their α_1-AT status. This may indeed reflect reluctance on the part of clinicians to consider a "COPD" pathology in a young patient without a substantial smoking history. However, diagnoses of asthma and α_1-ATD are not necessarily mutually exclusive. Is α_1-ATD a risk factor for asthma? The *SERPINA1* locus was not highlighted as a site of asthma-associated variation by genome-wide association study approaches, but this may not definitively disprove an association in individuals with α_1-ATD.

In a study of index and non-index cases of α_1-ATD, overall 37% had a physician diagnosis of asthma, and the value rose to 46% for index cases [185]. Once a diagnosis of COPD has been made, a finding of reversibility may be classified as an extra dimension of that disease spectrum rather than as an extra diagnosis of asthma. If similar reversibility were observed prior to establishment of fixed obstruction it would support this diagnosis. Moreover increases in atopy and IgE levels are reported in α_1-ATD [185]. A notable proportion of patients enrolled in the α_1-AT registry study group had evidence of FEV1 reversibility [186]. Childhood asthma is a risk factor for low FEV1 in later life [185] and, as in usual COPD, reversibility appears to be a marker of more aggressive development of airflow obstruction [187]. In one study cohort patients with the greatest degree of AHR had the lowest levels of circulating α_1-AT [187]. Bronchial hyperresponsiveness consistent with asthma may, therefore, be a phenotypic feature of the lung disease of α_1-ATD.

Excess COPD-associated cardiovascular risk

In usual COPD, an increased risk of ischaemic heart disease is proposed to result from a systemic inflammatory state [188]. As M α_1-AT is generally considered anti-inflammatory, a similar or enhanced relationship might reasonably be expected to arise in α_1-AT-associated emphysema. However, at present data on the relationship between α_1-ATD and cardiovascular disease give mixed signals and are therefore difficult to interpret. α_1-AT, specifically an oxidised form in complex with low density lipoprotein has been identified in atherosclerotic plaques [189, 190]. This species is a marker of smoking-related oxidative stress and has, therefore, been proposed as a putative mediator of smoking-associated vascular risk [191]. In population studies, both α_1-AT action and carriage of the Z allele have been associated with protective effects against cardiovascular disease [192–194]. In experimental studies, there are opposing reports on aortic stiffness, a surrogate marker of cardiovascular risk [195, 196]. Recent data have suggested that while systemic inflammation is elevated in the context of α_1-ATD lung disease compared with health, the increase may in fact be lower than that observed in usual COPD [197]. In our eyes, therefore, characterisation of the degree of extra cardiovascular risk associated with α_1-ATD lung disease requires more investigation.

Bronchiectasis

The interaction between α_1-ATD and bronchiectasis has been explored in various studies [198]. A study of 74 patients with α_1-ATD attending a specialist clinical service found that there was radiological evidence of bronchiectasis in 70 of these patients [199]. Twenty (27%) cases were classed as significant bronchiectasis based on a combination of radiological and symptom outcomes. Those with emphysema had more severe airway disease scores. A separate study identified no excess of α_1-ATD in bronchiectatic patients as a whole, but did find an association when it coexisted with emphysema [200]. This excess was due largely to PiZ patients. Additionally, compared with non-bronchiectatic common variable immune deficiency (CVID) control patients, CVID patients suffering with bronchiectasis had an increased burden of Z allele frequency in a small study [201]. It has been pointed out that the proportion of patients with bronchiectasis is similar to that of usual COPD. As such, bronchiectasis may be the result of emphysematous change in general, rather a specific predisposition of α_1-ATD [202].

Lung cancer

A relationship between *SERPINA1* allele state and the risk of developing lung cancer has been reported. Replicable observational studies suggest that the PiMZ state may be associated with increased risk of lung cancer, with some reports suggesting that there is as much as a 70% increase in risk (odds ratio 1.7). The histological subtypes appear to be adenocarcinoma and squamous cell carcinoma [203, 204].

Nevertheless, the genetic relationship between α_1-AT allele status and lung cancer is not entirely clear cut. Other studies have found no clear relationship between heterozygote status and lung cancer risk [205], or polymorphisms in *SERPINA1* and lung cancer [206]. However, the latter study was conducted in racially diverse populations and did not identify any relationship between *SERPINA1* polymorphisms and COPD. It may, therefore, have been underpowered to detect relationships between α_1-AT allele status and these diseases.

This suggested increased risk of lung cancer may be attributable to an increased propensity for α_1-AT heterozygote carriers to develop emphysematous change. Emphysema is a known risk factor for the development of lung cancer [207]. This fits well with studies indicating that the underlying histological subtype observed in usual COPD-related emphysema is squamous cell carcinoma [208]. It is proposed that the underlying mechanism is that lungs trap more carcinogens in the emphysematous state. However, in α_1-ATD other mechanistic possibilities for lung cancer progression may be supported by bench studies. Inhibition of neutrophil elastase prevented growth and metastasis of malignant cells introduced to immunodeficient mice [209]. α_1-AT can inhibit angiogenesis and tumour growth [210]. Separately, chemotherapeutic agents have been demonstrated to upregulate α_1-AT expression by cancer cells, and thereby protect against neutrophil elastase-induced tumour proliferation and progression [211]. Neutrophils seem to have a negative effect on proliferation, but increased effects on invasiveness. When pre-treated with α_1-AT, this effect of neutrophils on lung cancer cell lines is lost [212]. By contrast, elevated α_1-AT levels are associated with advanced disease and poor prognosis in lung cancer [213, 214]. Moreover, there is increased α_1-AT expression in chemotherapy resistant tumours [215].

Ongoing clinical and therapeutic issues in α_1-ATD

In parallel with these mechanistic questions, a range of issues remain unresolved in relation to existing optimal clinical care and development of novel therapies (figure 3).

Should we screen? If so, who should we test?

α_1-ATD is a frequently under-recognised and often misdiagnosed condition; current global estimates indicate that <10% of affected individuals have had a medical diagnosis of α_1-ATD. There are various reasons for this including the misconception that testing is expensive and complicated, poor awareness in the medical community regarding α_1-ATD, and the notion that α_1-ATD is a rarely encountered disease in the clinic. One approach to increase diagnosis, awareness and expertise in management would be to screen general populations for α_1-ATD, *e.g.* as part of standard neonatal testing. This was previously undertaken in Sweden where the incidence of α_1-ATD is particularly high, over a 2-year period. However, the findings from this did not encourage long-term adoption of this strategy [216]. Large proportions of parents of the children that screened positive for α_1-ATD experienced adverse psychological effects from the diagnosis and did not understand what the diagnosis meant and/or could not understand why it had been sought. This is understandable without clear offsetting benefits of access to a treatment that robustly impacted on the disease process, but interestingly it did not even appear to have any beneficial effect on parental smoking habits.

While only 1–2% of COPD cases were estimated to occur due to severe α_1-ATD in the 1980s [217], now, with the knowledge that intermediate deficiency is a contributing factor to the development of COPD [176], abnormal α_1-AT status is associated with up to 10% of COPD cases. These metrics strongly support the concept of a targeted screening strategy for people with COPD. Indeed, the American Thoracic Society (ATS), European Respiratory Society (ERS) and World Health Organization have all advocated targeted screening programmes in COPD sufferers for the detection of α_1-ATD [218, 219]. That said targeted screening is not the norm in all countries. Ireland, for example, has had a National Targeted Detection Programme since 2004. Anecdotal information from the programme coordinators together with accruing data from the Irish Alpha$_1$-Antitrypsin Deficiency Registry has yielded interesting new insights and information regarding opinions on screening, medical and public awareness of α_1-ATD, the true incidence of α_1-ATD in the Irish population [220] and previously unknown mutations [221].

Targeted screening has significant benefits over general population screening, which is more difficult to implement and expensive. By screening specific individuals with clinical characteristics associated with α_1-ATD the likelihood of detecting and diagnosing α_1-AT deficient individuals is much greater than it would be from a general screening programme. The ATS/ERS guidelines for diagnosis of α_1-ATD recommend testing in adults with: 1) symptomatic emphysema, COPD or asthma with airflow obstruction that is incompletely reversible with bronchodilators, 2) persistent obstruction on lung function tests and identifiable risk factors such as occupational exposure or cigarette smoking, 3) necrotising panniculitis, and 4) all individuals regardless of age with unexplained liver disease. In addition, the guidelines recommend that testing should also be discussed and could reasonably be accepted or declined in adults and/or adolescents with idiopathic bronchiectasis, persistent obstruction and c-ANCA-positive vasculitis. Predispositional testing is strongly recommended in siblings of α_1-ATD individuals, and is also considered important in all relatives of Z homo- and heterozygoytes and individuals with a family history of COPD or liver diseases not known to be attributed to α_1-ATD. The ATS/ERS task force did not recommend population screening or testing in adults with reversible asthma.

These guidelines were published over 10 years ago and should probably be refined and updated based on the wealth of new data regarding α_1-ATD that has emerged in the interim.

Does α_1-AT augmentation therapy work, and how would we know?

α_1-AT augmentation therapy trials in humans were initially published in the literature in the late 1980s. Since that date, α_1-AT augmentation has not been licensed for use in all developed countries with a high incidence of α_1-ATD. The variations in licensing reflect divergent opinions between clinicians and researchers regarding effectiveness of this expensive intervention. Initial licensing of augmentation therapy was based upon an assumption that its success in boosting circulating and lung levels of α_1-AT would be of clinically meaningful benefit. This assumption has subsequently been explored, and robust demonstration of such outcomes has proven problematic in trials, despite anecdotal accounts of major benefit to individuals who have received it [222]. A Cochrane review concluded there was insufficient evidence to justify its use [223], although other meta-analyses contend the opposite [224, 225]. A general issue with demonstrating benefit for any therapy in a relatively rare disease is the challenge of recruiting sufficient numbers to a trial that is suitably powered to robustly identify benefits that may be small but clinically relevant. Heterogeneity of disease behaviour, *e.g.* progression rates and emphysema distribution, in α_1-ATD may further mitigate against identifying a statistically significant treatment effect where this exists. The selection of appropriate readouts in terms of sensitivity, specificity, plausible mechanistic effects, and clinical utility is also not necessarily straightforward. We here explore some of the existing data using a range of different types of readout to illustrate these challenges, and ways in which they have been addressed.

Biochemical efficacy

Overall, biochemical data support the concept that augmentation therapy reverses loss-of-function mechanisms in α_1-ATD emphysema. The concept of a physiological threshold concentration of α_1-AT was supported by the basis of the apparent reduction in risk of emphysema in PiMZ (60% of normal circulating levels) relative to PiZZ (~15% of normal levels) individuals. CAMPBELL *et al.* [226] further demonstrated that the mean area of damage exerted by neutrophils was unrelated to α_1-AT concentration, until this level dropped below 10 μM. The working target for circulating α_1-AT levels to give adequate lung protection has therefore been widely accepted as 11 $\mu mol \cdot L^{-1}$ (~0.6 $g \cdot L^{-1}$).

Intravenous regimens of α_1-AT achieve the target serum concentration, and increase the epithelial lining fluid α_1-AT concentration above these protective thresholds [227]. There is a concomitant increase in anti-elastase activity and reductions in evidence of elastin breakdown in BAL and airway LTB4 burden [227–229]. Varying experience is reported regarding the effects of augmentation on urinary excretion of the elastin breakdown product desmosine [230, 231]. Isodesmosine was observed to decrease in BAL fluid following administration of intravenous and inhaled α_1-AT [231]. Measurement of more elastase-specific degradation products may show clearer effects. These are noted to be raised at exacerbation, suppressed by augmentation therapy and to correlate with spirometric severity of disease [232].

Effects of treatment on FEV1

Much effort has been put into trying to establish how biochemical efficacy may translate into clinical outcome benefit, with observational studies followed by randomised control trials and conflicting meta-analyses [223, 224]. In 1997, SEERSHOLM *et al.* [233] compared a cohort of patients in Denmark without augmentation therapy with a matched cohort in Germany receiving augmentation infusions. This study focused on FEV1, a traditional marker of COPD severity and progression. In patients with an FEV1 of 31–65% predicted, there was a modest but statistically significant benefit of augmentation therapy in terms of reducing FEV1 decline (21 $mL \cdot year^{-1}$). A year later, the National Institutes of Health reported on FEV1 change and survival in ~1000 patients known to be PiZZ or with significantly decreased (<11 $\mu mol \cdot L^{-1}$) α_1-AT [186]. This observational study noted that mortality was significantly reduced in the treatment group. There was no statistical benefit of α_1-AT augmentation therapy in terms of reducing FEV1 decline when considering the whole treatment group for whom serial FEV1 data were available. However, when patients were stratified by baseline FEV1, those with FEV1 35–49% predicted had significant benefit in terms of lung function protection from receiving α_1-AT augmentation. The reduction in decline of FEV1 was comparable (27 $mL \cdot year^{-1}$) to that observed previously. The next study observed rate of FEV1 decline in 96 α_1-AT deficient individuals prior to and subsequent to commencing augmentation [234]. A small, but statistically significant, benefit was observed in the rate of decline in the whole group following treatment (15 $mL \cdot year^{-1}$). The size of benefit increased in those with mildly impaired FEV1 (>65% predicted) and those declining most rapidly pre-treatment. These subgroups were small and regression to the mean effects cannot be excluded. A further observational study controlled for multiple variables in 164 PiZZ patients when comparing those receiving and not receiving augmentation [235]. Treatment was associated with modest stabilisation of FEV1 decline (by 47.6±33.5 mL·year^{-1}). Benefit was observed with ex-smoker status and, in contrast to the previous study, FEV1 <50% predicted. A mortality effect was not observed.

Neither of the two randomised controlled trials of augmentation therapy for which peer-reviewed analysis of FEV1 decline are available demonstrated benefit in this measure [236, 237]. However, a 2009 meta-analysis of augmentation therapy pooled observational and randomised controlled trials and was interpreted to support the concept of a group with moderately impaired FEV1 (35–65% predicted) deriving benefit [225].

Diffusion capacity

The use of FEV1 as a marker of disease progression in α_1-ATD-related emphysema is contentious. Increasing attention has been focused upon gas exchange (KCO) as an alternative lung function index. Breathlessness appears to occur in α_1-AT deficient patients before spirometric changes [238]. However, KCO decline is observed before FEV1 decline and may therefore be a better earlier measure [239]. It also continues to decline in severe disease after FEV1 has plateaued [187]. In this context KCO change may reflect further progression of emphysema and/or secondary pulmonary hypertension, but both processes will tend to associate with clinical deterioration. Impaired KCO and airflow obstruction are important independent determinants of health status in α_1-ATD [155]. Interestingly KCO correlates better between siblings with α_1-ATD than spirometry [240]. These findings support the concept that the emphysema of α_1-ATD may develop in concert with a direct attrition of the microvasculature [152]. Thus far, to our knowledge, KCO has not been used as a primary outcome measure in trials to assess the efficacy of α_1-AT augmentation. Therefore, it remains to be seen if it is able to better report a treatment benefit that many patients and clinicians describe than change in FEV1. There are two obstacles that may have hindered the adoption of KCO for this purpose. First, gas transfer measurements are less robustly reproducible relative to spirometric indices, thus an absolute difference of 15% is considered the threshold of significant change in the former, compared with 10% for the latter. Secondly, gas transfer measurements require more resources, as they require specialised lung function assessment techniques using more expensive equipment. This reduces the extent to which such testing is readily available outside specialist centres.

Lung densitometry

As there is a discrepancy between the results from spirometric and biochemical studies of augmentation therapy in α_1-ATD, lung density has been examined by CT scanning as an alternative marker of lung health. Density has been previously shown to be more sensitive than FEV1 in detecting emphysema progression [241, 242]. It has not been extensively validated as a correlate of clinically significant progression of emphysema in α_1-ATD, but it may be better than FEV1 in predicting mortality in α_1-AT deficient patients [243]. In a combined analysis of the only two randomised control trials examining augmentation therapy, patients in the augmented group suffered significantly less loss of lung density [224]. The magnitude of benefit may be greater if statistical analyses of lung densitometry change are confined to lower lobes of the lung where, classically, most damage occurs [244]. Data from a further prospective randomised controlled trial into the use of intravenous α_1-AT augmentation (NCT00261833) have been reported [245]. This trial found that lung density declined less rapidly in the treatment group, by a measure that represented one component of the primary end-point (CT-quantified decline in total lung capacity) but not in the pre-specified composite measure.

Exacerbations and patient-centred outcomes

Does augmentation therapy benefit function and quality of life in a quantifiable way? There appears to be a paucity of information regarding the impact of augmentation on general health status and patient perceived benefit. Current trials of intervention in usual COPD typically focus on a range of indices beyond lung function when considering benefit of an intervention. Measures such as 6MWT, dyspnoea scores, overall patient symptom scores such as the COPD assessment test and St George's Respiratory Questionnaire (SGRQ) seem less utilised, to date, in α_1-AT augmentation studies. An exception to this is the questionnaire-based study that indicated a substantial reduction in the incidence of patient-reported exacerbations following commencement of augmentation therapy [246]. Furthermore, in a randomised control trial of augmentation therapy, while augmentation was not associated with a benefit in terms of the SGRQ, the severity of exacerbations was reduced in patients receiving augmentation [236]. Exacerbation reduction is important when considering both the impact on the patient's day-to-day quality of life and also when considering preservation of lung health, since exacerbations are associated with ratcheted decline and increased mortality [247, 248].

Can we improve delivery?

Aerosolized α_1-AT augmentation achieves acceptable delivery to the periphery of the lung in moderate disease states [249], and delivery of the drug may be optimised by different systems that are personalised for the patient's breathing patterns [250]. Inhaled α_1-AT does reach the lung interstitium of exposed subjects [251]. In humans, there is evidence of biochemical efficacy. Aerosolized α_1-AT reduces neutrophil elastase activity as determined by bronchoscopic sampling [252], and in CF patients exposed to inhaled α_1-AT there is evidence that airway inflammatory load is reduced [126]. There is a need for subsequent trials in inhaled α_1-AT augmentation therapy to examine the efficacy between different degrees of airway obstruction. Scintigraphy studies with radiolabelled α_1-AT have led to somewhat contradictory conclusions. In one, lower FEV1 was associated with central rather than peripheral deposition in lung tissue [253]. In another study, using a controlled inhalation technique [254], the distribution of lung deposition was independent of FEV1. A phase 2/3 study has supported the safety of the aerosolised α_1-AT formulation currently in development [255].

Aerosolized α_1-AT may represent a more acceptable form of therapy for patients [256], and may address the issue of affordability currently challenging α_1-AT augmentation therapy. Intravenous augmentation therapy contains substantial proportions of inactive material [36]. There is therefore potential to improve the proportion of native, active material and extend its half-life in the circulation. This could be achieved through optimised preparation methods and the addition of small molecules to stabilise the active conformation.

Can we assess cost-effectiveness of augmentation?

α_1-AT augmentation therapy is costly at ~$100 000 per year [257]. The cost-effectiveness of α_1-AT augmentation has not been extensively examined. Early work suggested that the cost of augmentation per life year saved might be equivalent to other commonly treated conditions, *e.g.* hypertension treatment and coronary artery bypass grafting [258]. However, these assessments were carried out before outcome data were available and now appear overly optimistic. More recently, an interesting comparison was made between augmentation therapy for life or until FEV1 <35% predicted and gold standard therapy without augmentation [259]. The measure used was QALYs; a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance. Treatment for life yielded 7.19 QALYs and cost $895 243. Treating until FEV1 was below 35% predicted cost $511 930 and produced 6.64 QALYs. Gold standard therapy without augmentation cost $92 091 and gave 4.62 QALYs. The incremental cost-effectiveness ratio was $207 841 per QALY for augmentation until FEV1 is below 35% predicted and $312 511 per QALY for the augmentation therapy for life strategy. These results indicate a large increase in cost, for relatively little increase in quality of life preservation. Some authors point towards the possible reduction in exacerbations as an offset cost saving benefit of augmentation. Exacerbations are probably responsible for the largest burden of healthcare costs for usual COPD in terms of their acute management and long-term sequelae with frequent exacerbators demonstrating accelerated decline [247, 248, 260]. In α_1-ATD the cost–benefit implications of the apparent reduction in exacerbation frequency and severity remain to be quantified.

Is there a role for subspecialist centres?

Internationally a number of subspecialist clinical centres have been established with a special interest in managing the follow-up and care of individuals with α_1-ATD. These centres may operate on a multidisciplinary basis, *e.g.* with input from respiratory, hepatology, paediatric and clinical chemistry specialists.

Such subspecialist centres are potentially highly beneficial for improved clinical care, research progress and the interface between these. Subspecialist centres and multidisciplinary care have been show to improve patient outcomes in other diseases [261, 262]. α_1-ATD is a relatively rare disease even within the general respiratory outpatient population. As a result, even specialist respiratory physicians may have limited understanding of the condition and so there is a case for establishing expert referral centres [263]. In addition, the importance of joint care with hepatology is well illustrated by autopsy studies showing an excess of histopathologically significant disease on autopsy that was unreported clinically [264]. Following an initial peak of presentations with liver disease in early childhood, the subsequent incidence increases with age. Integrating systematic, specialist hepatology follow-up with respiratory care allows this to be monitored routinely.

The benefits of subspecialist care integrated with research studies for the development of personalised care are well illustrated by the case of a man identified as a compound heterozygote for the Z allele and a novel variant of α_1-AT [28]. The characterisation of the biochemical behaviour of the novel variant has implications for the clinical advice that can be given to the individual and family members. Such cross-talk between clinical experience and research centres also opens new research avenues. Moreover, it provides a readily identifiable focus for recruitment into trials of new therapeutic strategies that are urgently needed in α_1-ATD. However, the absence of a therapeutic intervention robustly proven to benefit clinical outcomes renders the justification of such services on cost–benefit grounds challenging.

Which new therapeutic options are feasible and what are the challenges faced?

Drug development for orphan/rare diseases such as α_1-ATD is covered by less stringent legislative requirements in Europe and the USA than is the case for treatments for other diseases. This is in recognition of the practicalities surrounding the numbers of patients that can be recruited for trials in these smaller populations. It also partially offsets the disincentive for a commercial organisation to develop a drug for a relatively small market. Nevertheless, the standard hurdles to the development of a new therapy still pertain: sufficient preclinical promise must be shown to then enter clinical trials where safety and efficacy must be demonstrated, before regulatory approval is sought. Repurposing of existing therapies, that are already approved for other clinical indications may be of some benefit in this. For instance, the boosting of autophagy pathways by carbamazepine has been shown to have beneficial effects on hepatic polymer clearance in a transgenic PiZ mouse model [265]. The doses used in these studies appear to equate to far higher doses than the current therapeutic regimens used in humans. However other drugs, *e.g.* rapamycin, may offer similar potential benefit through increasing autophagy with doses that within those currently used in humans [266]. Clinical trial data are required to further evaluate the risk–benefit ratio of such an approach.

We now focus on nucleic acid based, inducible pluripotent stem cell (iPSC) and small molecule strategies to develop entirely new therapeutic agents specifically for use in α_1-ATD.

Nucleic acid strategies

As with all single gene disorders, nucleic acid-based therapies have relevance for α_1-ATD. Gene therapies to treat either the liver or lung manifestations of the disease are at various stages of development. For the liver disease, approaches that have been considered include ribozymes, antisense peptide nucleic acids, and small-interfering (si)RNAs; all designed to inhibit expression of the mutant gene (reviewed in [267]). For the lung disease, various non-viral and viral delivery approaches designed to express the normal gene either locally or intramuscularly in an attempt to increase α_1-AT levels in the circulation above the deficiency threshold have been reported [268–272]. Newer approaches are focused on coupling haematopoietic stem cell therapy with α_1-AT cDNA-lentiviral gene therapy [273, 274]. A recent phase 2 clinical trial demonstrated that intramuscular administration of the gene therapy to α_1-AT deficient individuals increased serum levels of vector (adeno-associated virus (AAV)) derived normal human α_1-AT to $>20\ \mu\text{g mL}^{-1}$ [275]. This study supported the feasibility and safety of adeno-associated virally administered gene therapy for α_1-ATD, but highlights the relatively modest increments in systemic levels that such approaches have achieved to date. The reasons for this are not entirely clear at present, but do not seem related to immune-mediated rejection. Indeed the sites of vector administration and related α_1-AT expression appear to induce co-localisation of AAV capsid specific regulatory T-cells (Tregs) that will tend to be tolerogenic [276]. Further studies are evaluating intrapleural administration of a replication-deficient AAV-α_1-AT virus to individuals with α_1-ATD [277]. In the past few years RNA interference methods to knock-down production of Z α_1-AT have developed rapidly. Constructs showing effectiveness in animal models of liver disease are now commencing phase 1 and 1/2 clinical trials [278, 279]. These utilise siRNAs that bind to the 3′ untranslated region of SERPINA1 mRNA transcripts and target them for degradation, and couple these with hepatocyte targeting moieties.

ER stress and the UPR in lung-resident inflammatory cells may contribute to inflammatory consequences in α_1-ATD [59]. Alterations in the epigenome affecting microRNA expression and DNA methylation may play a role in this. microRNAs (miRNAs) are RNAs that negatively regulate gene expression. HASSAN *et al.* [280] profiled the miRNA expression pattern in monocytes from MM and ZZ homozygotes. 43 miRNAs were detected with significant differential expression between the two groups. miR-199a-5p was the most highly increased miRNA is asymptomatic ZZs, by 50-fold compared with MMs. Its levels were lower in MMs and ZZs with COPD and this was associated with hypermethylation of the miR-199a-2 promoter (miR-199a-2 encodes miR-199a-5p). Components of the UPR including Grp78, ATF6, p50 and p65 were determined to be valid targets of miR-199a-5p and their expression was higher in people with COPD leading to an increased UPR. Finally miR-199a-5p overexpression was shown to decrease UPR and also impact on exaggerated basal and LPS-induced cytokine expression. In summary, miR-199a-5p was found to be decreased in COPD due to promoter methylation suggesting that miRNA or epigenetic-based therapies may have relevance for COPD in α_1-AT deficient or α_1-AT replete individuals.

How can this insight be exploited? One option is to consider therapeutic modulation of miRNA using either inhibition or augmentation strategies [281]. However, there are a number of important caveats that need to be considered when planning miRNA modulation strategies for α_1-ATD. For example by inhibiting miRNAs that regulate α_1-AT, its expression can be increased within the liver or locally in the lung; however, because the α_1-AT that will be expressed is the Z form it will have impaired anti-elastase activity and will be prone to polymerisation. Another approach could be to use miRNA mimics based on the miRNAs that regulate elastase expression, and thus decrease the protease burden within the PiZ lung. However, because neutrophils are terminally differentiated cells these miRNA mimics would need to be stably targeted to immature cells in the granulocyte lineage; apart from being a challenging task this could also have unpredictable systemic effects.

In the context of the lung disease associated with α_1-ATD, an miRNA modulation strategy that increased the antiprotease protective screen within the Z α_1-AT lung could be effective. Secretory leucoprotease inhibitor (SLPI) is a major lung serine antiproteinase that inhibits elastase. It is expressed by monocytes and airway epithelial cells and is regulated by miRNAs [282]. In order for α_1-AT augmentation therapy to be fully effective it is required to deposit in the lower airways. Therefore, any alternative augmentation strategy should also be effective in the alveoli. SLPI is expressed by both bronchial [282] and alveolar airway epithelial cells [283–285]. miRNA-based therapy to augment endogenous SLPI expression would need to target both of these cell types.

Previous studies have looked at the potential of SLPI as a therapeutic for α_1-ATD lung disease and have examined the behaviour of SLPI *in vivo*. Although recombinant SLPI is degraded in the α_1-AT deficient lung [286], endogenous SLPI does not appear to be; this may not be entirely true given what is known about degradation of SLPI in the COPD lung. While SLPI levels are actually slightly increased in the PiZ *versus* PiM lung, SLPI activity could be impaired [287]. A miR-based SLPI augmentation approach, if successful, could have therapeutic potential not only for ZZ homozygous individuals with lung disease but also MZ individuals who develop lung manifestations due to cigarette smoking. Furthermore, if combined with methods to increase miR-199a5p expression, disease pathways mediated by exaggerated UPR and cytokine expression could also potentially be controlled.

iPSC-based approaches

α_1-ATD has been at the forefront of the application of iPSC technology to studies of disease and therapeutic development [288–290]. The demonstration that skin fibroblasts from PiZZ individuals could be induced *via* an iPSC state to form hepatocyte-like cells that recapitulated the disease phenotype was a milestone in the development of such technology [289]. A further landmark moment came with the use of highly targeted gene editing to correct the Z mutations in such cells [288]. This allows the study of syngeneic PiMM and PiZZ hepatocyte-like cells. The therapeutic potential of this technology to make "corrected" PiMM cells that will avoid immune rejection on their return to the patient from whom the cells are derived is exciting and is currently being developed. In an ideal case, "corrected" hepatocytes might engraft and repopulate the liver by outcompeting PiZZ cells, but it remains an open question whether this could occur without further intervention. Challenges include optimising homogeneity and differentiation of such cells into mature hepatocytes, and guarding against the risk of malignant transformation.

Peptide and small molecule strategies

The combination of loss- and gain-of-function drivers of lung and liver disease in α_1-ATD provide an inherent challenge to the development of a single "magic bullet" therapy for patients. Augmentation of functional α_1-AT levels through exogenous infusion or endogenous synthesis of the wild-type protein, or alternatively boosting alternative antiprotease levels has the potential to address the former pathways. Blocking synthesis or increasing clearance of deficiency-variant α_1-AT protein can address the latter. There is, therefore, a high probability that combination approaches will be required for optimal therapy in future.

However, since loss- and gain-of-function in α_1-ATD is driven by protein misfolding and aberrant conformational change, addressing this behaviour may counter both pathogenic cascades at source. One recent strategy for this has used a high-throughput approach to target the network of proteostatic mechanisms that cells have already evolved. This rationale has identified a compound, the histone deacetylase 7 inhibitor suberoylanilide hydroxamic acid (SAHA), as an agent capable of restoring Z α_1-AT secretion from epithelial cells [291].

Alternatively, the insights gained from structural studies of α_1-ATD have led to the development of a range of strategies to modulate the conformational behaviour of α_1-AT by targeting it directly. This is analogous to the strategies pursued to rescue folding and stabilise functional conformers in CF, with striking translational success [292, 293]. For α_1-ATD the aim is to stabilise the native conformation and/or limit the population of polymerogenic intermediates and/or block intermolecular insertion of complementary structural motifs by ligand binding [28, 29]. Broadly, three approaches have been pursued: 1) annealing of peptide analogues of the reactive loop to its insertion site in β-sheet A [20, 294–297]; 2) hypothesis-based targeting of allosteric sites [298, 299]; and 3) targeting of druggable sites identified by hypothesis-free computational approaches [300].

Peptide-based strategies have crystallographic validation for the specificity of ligand binding to the targeted site from structures of α_1-AT and other serpins with peptides annealed at the s4A position. While they are highly effective at blocking and even reversing polymerisation *in vitro*, in cell-free systems, they face challenges in their effective delivery *in vivo*. Peptide therapies cannot be given orally in order to avoid digestion in the gastrointestinal tract, and would have to be delivered to the ER to rescue folding. Moreover, reactive loop analogues tend to bind to give complexes with α_1-AT that are highly stable and inactive as antiproteases. Such an interaction would counter the toxic gain-of-function of polymerisation but not the associated loss-of-function that drives liver disease in α_1-ATD. Promising findings have been reported in a number of these regards when a short, N-terminal acetylated peptide (Thr-Thr-Ala-Ile) has been used. However, it may be that this approach is best developed further by the identification of peptide mimetic compounds with more favourable characteristics for use as drugs.

The best characterised allosteric site to be targeted in a hypothesis-based approach, to date, is a solvent accessible hydrophobic pocket that lies lateral to β-sheet A in the native conformation. This is filled and sealed during polymerisation. Site directed mutagenesis and crystallography studies have demonstrated the therapeutic promise of blocking this site with a small molecule. Indeed a cavity-blocking mutant (Thr114Phe) of α_1-AT can achieve the therapeutically desirable combination of inhibiting polymerisation without abolishing its inhibitory activity. Based on such findings, *in silico* targeting, followed by *in vitro* and *in vivo* validation identified a compound named CG that blocked intracellular polymer accumulation. However, the interaction of CG with α_1-AT abolishes inhibitory activity, and despite extensive efforts, to date, no crystal structure has validated whether it acts by binding at the target site. Hypothesis-free strategies to identify and target further allosteric sites have shown some encouraging early promise for computational strategies that can reveal more cryptic sites in α_1-AT. *In silico* hits have been validated by cell-free *in vitro* studies showing that they interact with α_1-AT. However, as yet, such approaches have not been shown to work in cells.

In all these cases the need to develop small molecules targeted at isolated protein chains into therapies that may work in far more complex environments *in vivo* represents a major hurdle within preclinical development. This may be overcome by the brute force approach of truly high-throughput initial screens. In addition small molecule stabilisers of purified α_1-AT in the native conformation could be used to improve the function and lifespan, and hopefully therefore the effectiveness, of augmentation therapy. However, technical advances mean that initial screens can now use live cell models of α_1-ATD rather than purified protein to identify potential lead compounds to address the underlying molecular mechanisms of misfolding and polymerisation. This “cells first” approach has the advantage that hits will be biologically validated in terms of appropriate bioavailability across cell and organelle membranes, and achieving a physiologically relevant outcome in a cell-based system. Hits can then be interrogated to identify specific actions within the protein folding, stabilisation or degradation systems, before being assessed in secondary screens together with derivatives optimised for such activities.

Conclusion

At first glance the principal aetiological factors for lung disease in α_1-ATD are apparently clear-cut. Monogenic defects lead to a protease–antiprotease imbalance favouring dysregulated elastase activity in an organ in which elastin is a major connective tissue component. A general mechanism for the associated liver disease seems well supported by experimental evidence that correlates with clinicopathological observations. The existence of controversies, unresolved questions and active debate in such a well-defined field may therefore seem surprising. The live issues reflect the drive to better understand the basis for clinical needs that are unmet by current treatment options. However, they also relate to the powerful insights gained by 50 years of cross-talk between leading-edge basic/translational scientific research and clinical experience. The mechanisms of α_1-ATD have been tracked from the genetic to epigenetic, protein, cellular, tissue, organismal, and population levels. They can be characterised across multiple scales of time (microseconds to millennia) and space (atomic to human) and they are exacerbated by environmental factors. It is therefore highly suitable for the application of new investigational approaches as these are developed within diverse disciplines. The field has been increasingly illuminated as a result, with discoveries effectively answering many questions as they were initially understood.

However, they have gone on to define new issues of relevance not only to treating α_1-ATD, but also to many other areas of lung pathobiology and to analogous disorders caused by misfolding and conformational change. The recognition of similarly open questions in α_1-ATD management and service configuration and the identification of effective strategies to address them may be of particular significance to other rare diseases.

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The asthma–COPD overlap syndrome

Miriam Barrecheguren, Cristina Esquinas and Marc Miravitlles

Case history: A 58-year-old female presents with exertional breathlessness and spirometry shows post-bronchodilator FEV_1 of 69% predicted and FEV_1/FVC of 0.63. The bronchodilator test showed an increase in FEV_1 of 316 mL and 15%. She is a smoker of 10 cigarettes a day (18 pack-years) and reports frequent episodes of bronchitis with wheezing during childhood that were treated with parenteral corticosteroids and occasionally with antibiotics. Is this chronic asthma, COPD or another entity, and how does it alter her management?

Chapter summary: In the spectrum of chronic airway disease, some individuals share characteristics of asthma and COPD. The ACOS has been defined as symptoms of increased variability of airflow in association with non-fully reversible airflow obstruction. ~15–20% of COPD patients may have ACOS and patients with ACOS present increased reversibility of airflow obstruction, more eosinophilic bronchial and systemic inflammation and increased response to ICSs, compared with the remaining patients with COPD. Patients with ACOS have more frequent exacerbations, more wheezing and dyspnoea and more severely impaired health status compared with COPD. From the clinician's point of view, the relevance of the ACOS is to identify patients with COPD who may have underlying eosinophilic inflammation that responds to ICSs. So far, no biomarker has been identified that allows the differentiation of ACOS from COPD, but intense investigation is being conducted to better characterise these patients at both primary and secondary healthcare levels.

The patient in the case history is a 58-year-old female with COPD. She fulfils all the criteria for COPD: smoker of >10 pack-years, exertional dyspnoea and post-bronchodilator FEV_1/FVC <0.7. However, this case has some particular characteristics: the patient has a history of episodes described as "bronchitis" in childhood, which improved with corticosteroids, and she has a clearly positive bronchodilator test. Both characteristics could be compatible with bronchial asthma. This is an example of a patient that shares the characteristics of both asthma and COPD and could be classified as having ACOS. This diagnosis has implications for management, because bronchodilators are necessary to treat the COPD component and ICSs are necessary to treat the asthmatic component.

In the spectrum of chronic airway diseases, asthma and COPD are, by far, the most frequent. Although they have clear differences, some manifestations of both may coexist in

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a given patient, and this has been called ACOS. This syndrome may correspond to the description of an asthmatic smoker who has developed chronic airflow obstruction; however, previous history of asthma is occasionally not known and the lack of specific biomarkers makes the diagnosis of ACOS difficult.

After having recognised that response to ICSs in COPD is poor, and that the use of long-term ICSs at high doses is associated with an increased risk of adverse effects, there has been a growing interest in identifying COPD patients who may respond to ICSs [1]. Characterisation and better definition of ACOS may help to identify a subgroup of patients with COPD that responds to ICSs, in contrast to most of the patients with COPD, who present a predominantly neutrophilic inflammation that is resistant to ICSs [2].

In the last few years there has been increasing interest in characterising the different phenotypes of COPD [3], among which the ACOS is a clear example that fulfils all the criteria for a clinical phenotype of COPD, including different outcomes and response to treatment [4]. The need for a specific therapeutic approach to ACOS justifies the implementation of clear diagnostic criteria.

Definition of ACOS

Characterising the ACOS from the perspective of both COPD and asthma has been an area attracting increasing attention in recent years. Some authors have defined the ACOS as symptoms of increased variability of airflow in association with non-fully reversible airflow obstruction [5]. More recently, LOUIE *et al.* [6] defined the ACOS as one of two clinical phenotypes: 1) asthma with partially reversible airflow obstruction, with or without emphysema or reduced *D*LCO to <80% predicted; and 2) COPD with emphysema accompanied by reversible or partially reversible airflow obstruction, with or without environmental allergies or reduced *D*LCO. IZQUIERDO-ALONSO *et al.* [7] identified ACOS patients as having COPD (>10 pack-years of smoking and post-bronchodilator FEV1/FVC <0.7) and a personal history of asthma before the age of 40 years, with the addition of normal *D*LCO and the absence of pulmonary emphysema demonstrated by imaging techniques.

Guidelines have also addressed the diagnosis and treatment of subjects with mixed disease. The Canadian guidelines of 2007 specified that “if the asthma component (in COPD) is prominent, earlier introduction of ICSs may be justified” [8]. Later, in 2010, the Japanese guidelines of COPD dedicated a chapter to “Treatment of COPD complicated by asthma” [9] and indicated that ICSs combined with long-acting β_2-agonists (LABA) should be the first-choice treatment irrespective of the level of airflow obstruction.

The Spanish guideline for COPD (GesEPOC) identified four different phenotypes with clinical relevance and specific therapeutic approaches, one of which was the ACOS [10]. Considering the lack of general agreement in relation to the diagnosis of ACOS, a group of experts proposed diagnostic criteria in a consensus document [11]. These Spanish consensus criteria were as follows. 1) Major criteria: very positive bronchodilator response (>400 mL and >15% in FEV1), sputum eosinophilia or previous diagnosis of asthma. 2) Minor criteria: increased total serum IgE, previous history of atopy or positive bronchodilator test (>200 mL and >12% in FEV1) on at least two occasions [11]. To be diagnosed with ACOS, a patient must fulfil two major or one major and two minor criteria. The new Finnish guidelines for the treatment of COPD proposed the same criteria as those of the Spanish guidelines for the diagnosis of ACOS, with the addition of an elevated *F*eNO >50 ppb as a major criterion and a peak flow follow-up typical for asthma as a minor criterion [12]. The latest Czech Republic guidelines, published in June 2013, also include the ACOS with its own diagnostic criteria, similar to the Spanish guidelines [13]. These are quite restrictive criteria and represent a very conservative approach until more evidence from large clinical trials becomes available on the characterisation and differential response of the overlap phenotype. In fact, two recent studies in Spain using the previous criteria identified only 5–6% of patients fulfilling the criteria for ACOS in patients with smoking-related COPD (table 1) [20, 21]. This percentage is clearly below the expected number of individuals sharing the characteristics of asthma and COPD according to epidemiological data.

In 2014, the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) published a joint document on ACOS [23]. ACOS was defined as the presence of persistent airflow limitation with several features usually associated with asthma and other features usually associated with COPD. The document presents a list of features of either asthma or COPD and suggests that ACOS may be diagnosed when a similar number of features of asthma and COPD are identified in a given patient. Although this approach is intuitive, it is also quite imprecise because it does not indicate how many of these features are necessary and/or whether they have the same relevance for the diagnosis of ACOS. An example is the presence of heavy exposure to tobacco smoke as one of the features that favour COPD. However, in our opinion, smoking (or exposure to biomass fuels) is a necessary factor for the diagnosis of ACOS; persistent airflow obstruction in a never-smoking individual cannot be diagnosed as ACOS. In this case the diagnosis is chronic asthma with non-reversible airflow obstruction, but no overlap with COPD can be postulated if there is no significant exposure to inhaled risk factors. Asthma is recognised as a risk factor for developing chronic non-fully reversible airflow obstruction, but in the absence of additional risk factors (smoking or exposure to dusts or fumes) it will be chronic asthma, not ACOS. A completely different situation is a young asthmatic who smokes and, as a consequence, the reversible airflow obstruction of asthma becomes non-fully reversible. It is clear that smoking does not cure asthma; instead, smoking asthmatics are at increased risk of developing chronic airflow limitation. However, the chronic airflow limitation (or COPD) developed in smoking asthmatics has some particular characteristics different from those of non-asthmatic smokers who develop COPD. In smoking asthmatics with chronic airflow limitation, bronchial hyperresponsiveness (BHR), greater IgE sensitisation, higher plasma levels of total IgE, more wheezing and more allergic rhinitis are more frequent compared with COPD developed in non-asthmatic smokers [24]. These “asthmatic smokers with COPD” fulfil the profile of patients with ACOS.

Due to its simplicity, it would be relevant to verify whether previous diagnosis of asthma before the age of 40 years in a smoker with COPD would be sensitive enough to identify ACOS. There is a concern that asthma may have been underdiagnosed or misdiagnosed in childhood or adolescence or that the patients simply do not remember the diagnosis of previous respiratory problems. In addition, there is the possibility that the asthmatic component of an ACOS patient remained unnoticed until late in life, but this patient would, in any case, be classified as having ACOS. More research is required to establish the best criteria for the diagnosis of ACOS in COPD patients.

Clinical characteristics of ACOS

Clinically, the ACOS usually corresponds to COPD patients with increased reversibility and/or asthmatics with a history of smoking who develop non-fully reversible airway obstruction at an

Table 1. Prevalence of ACOS in COPD patients according to different diagnostic criteria

	Year	Country	Prevalence %	Criteria
Database studies				
Soriano [14]	2003	USA and UK	52	Self-reported physician diagnosis of COPD and asthma
Rhee [15]	2014	Korea	54.5	Diagnosis of COPD and asthma
Marsh [16]	2008	USA	55	Combinations of chronic bronchitis, emphysema and asthma, with and without non-fully reversible airflow obstruction
Clinical studies				
Miravitlles [17]	2013	Spain	17.4	Previous diagnosis of asthma before the age of 40 years
Menezes [18]	2014	Latin America (Brazil, Venezuela, Chile, Mexico and Uruguay)	11.6	Post-bronchodilator FEV_1/FVC <0.7 and asthma (wheezing in the last 12 months plus post-bronchodilator increase in FEV_1 or FVC of 200 mL and 12% or "medical diagnosis of asthma")
Hardin [19]	2011	USA	13	Previous diagnosis of asthma before the age of 40 years
Louie [6]	2013	USA	15.8 (pulmonary clinic); 24.3 (asthma clinic)	1) Asthma with partially reversible airflow obstruction, with or without emphysema or D_{LCO} <80%; or 2) COPD with emphysema accompanied by reversible or partially reversible airflow obstruction, with or without environmental allergies or reduced D_{LCO}
Izquierdo-Alonso [7]	2013	Spain	12	D_{LCO} >80%, absence of pulmonary emphysema on CT or chest radiograph and personal history of asthma before the age of 40 years
Miravitlles [20]	2014	Spain	5.8	Spanish consensus criteria[#]
Golpe [21]	2014	Spain	21.3 (biomass-related COPD); 5 (smoking-related COPD)	Spanish consensus criteria[#]

[#]: two major or one major and two minor criteria among the following. 1) Major criteria: very positive bronchodilator response (>400 mL and >15% in FEV_1), sputum eosinophilia or previous diagnosis of asthma. 2) Minor criteria: increased total serum immunoglobulin-E, previous history of atopy or positive bronchodilator test (>200 mL and >12% in FEV_1) on at least two occasions [11]. Reproduced and modified from [22] with permission from the publisher.

older age (figure 1) [25, 26]. It has been demonstrated that asthma, active smoking and atopy interact in the development of fixed airflow obstruction. There is a synergy that affects atopic ever-smokers with asthma who develop COPD with particular inflammatory and clinical characteristics [27]. These individuals usually share characteristics of both diseases, making it difficult to classify them as having asthma or COPD in everyday clinical practice [28].

But why is it so important to identify patients with ACOS? ACOS patients have more frequent exacerbations compared with patients with COPD [17–19]. They also have more respiratory symptoms, such as dyspnoea and wheezing (but not more cough and sputum), and reduced physical activity compared with COPD alone [17]. ACOS patients have a lower self-rated health and more impaired health-related quality of life compared with COPD [29, 30] and particularly with non-exacerbators with COPD [20]. As a consequence, ACOS patients consume from two- to six-fold more healthcare resources than asthma or COPD patients [31].

Some features can help us identify ACOS. In patients with COPD, increased reversibility is one of the key differential aspects of individuals with ACOS [32]. BHR is common in asthma, especially in patients with active symptoms, but BHR is frequently asymptomatic and has been shown to be a risk factor for developing COPD [5]. In fact, BHR can be demonstrated in up to two-thirds of COPD patients [33] and, in patients with established asthma or COPD, more severe BHR is associated with more severe symptoms and a more rapid decline in FEV_1. Consequently, some authors recommend the use of provocation tests with agents that do not cause direct airway smooth muscle contraction, such as histamine, mannitol or hypertonic saline, to diagnose ACOS in patients with COPD [34].

Inflammatory characteristics and genetic markers of ACOS

The key issue in the characterisation of ACOS patients is to identify whether they have a different inflammatory pattern compared with the remaining patients with COPD. Inflammation in asthma patients is considered to be mainly eosinophilic while in COPD it is neutrophilic [35].

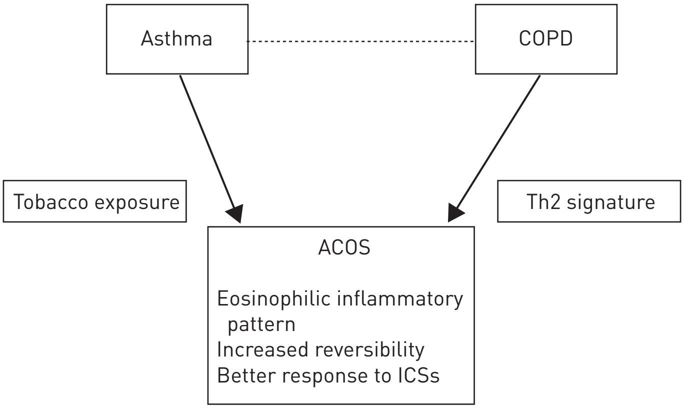

Figure 1. Clinical expression of the ACOS. The ACOS usually corresponds to a smoking asthmatic patient who develops non-fully reversible airway obstruction and/or a COPD individual (with or without a known history of asthma) with a T-helper cell (Th) type 2 signature (increased blood and lung eosinophilia, increased AHR and better response to ICSs).

Different inflammatory patterns have been described in patients with a diagnosis of ACOS. Ghebre *et al.* [36] identified sputum cytokine profiles in asthma and COPD patients using factor and cluster analyses. Three biological clusters were identified in this population: 1) asthma predominant with eosinophilia and high T-helper cell (Th) type 2 cytokines; 2) subjects with asthma and COPD with sputum neutrophil predominance; and 3) COPD predominant with mixed neutrophilia and eosinophilia.

However, more studies have related ACOS with eosinophilic inflammation in COPD. In a recent study, Christenson *et al.* [37] investigated whether asthma-associated gene signatures were increased in a subgroup of COPD patients and associated with asthma-related features, in other words, with ACOS. The hypothesis was that, although inflammation in COPD is typically driven by type 1 (Th1) immune responses, asthma-associated inflammatory pathways (*e.g.* eosinophilia and Th2 inflammation) may underlie the disease in some patients. This COPD subgroup (ACOS), in which these asthma-associated inflammatory pathways play a more significant role, may also benefit most from ICSs. In asthma, the subgroup of patients with the highest airway epithelial expression levels of genes associated with Th2 (the "Th2 high" endotype) has higher IL-5 and IL-13 expression levels in bronchial biopsies, increased serum total IgE levels, greater blood and lung eosinophilia, increased AHR and better lung function response to ICSs [38, 39]. In their study, Christenson *et al.* [37] developed a 200-gene signature of the Th2-related gene expression, the Th2 signature (T2S) score, which correlated well with Th2-associated clinical characteristics in asthmatic patients, and found that ~20% of their COPD patients had increased expression of T2S. They next investigated the association of T2S with clinical parameters in the GLUCOLD (Groningen and Leiden Universities study of Corticosteroids in Obstructive Lung Disease) cohort of patients with COPD [40]. T2S was significantly associated with increased tissue eosinophil numbers, increased serum eosinophil percentage and increased bronchodilator responsiveness. Interestingly, a higher T2S was associated with greater hyperinflation improvement after ICSs (with or without LABA) treatment *versus* placebo at 30 months [37]. This study suggests that T2S may serve as biomarker to identify ACOS patients who will benefit from ICSs treatment.

Previous studies have investigated eosinophilic inflammation in ACOS. In a study that compared stable COPD patients with concomitant asthma with the remaining COPD patients, peripheral and sputum eosinophil counts were significantly higher in the first group [41]. Since sputum eosinophilia is not routinely determined in clinical practice, indirect markers of this type of inflammation have been investigated. Chou *et al.* [42] demonstrated higher levels of *F*eNO in patients with COPD and eosinophilic airway inflammation (>3% eosinophils in induced sputum), with a cut-off of 23.5 ppb of *F*eNO having a sensitivity of 62.1% and a specificity of 70.5% for the identification of eosinophilic inflammation.

In the search for other plasma and sputum biomarkers of ACOS, Iwamoto *et al.* [43] investigated four potential biomarkers in COPD (surfactant protein A (SP-A), soluble receptor for advanced glycation end products (sRAGE), myeloperoxidase (MPO) and neutrophil gelatinase-associated lipocalin (NGAL)). Compared with asthma patients, sputum MPO and plasma SP-A were significantly elevated in ACOS, while only sputum NGAL was significantly increased compared with COPD. Fu *et al.* [44] examined the levels of the systemic inflammation markers CRP and IL-6 in asthma, COPD and ACOS patients and identified potential clinical characteristics that were associated with these biomarkers. They found a high prevalence of systemic inflammation in older people with ACOS and an elevated IL-6 compared with asthma patients. Age, the Charlson comorbidity index and

IL-6 were independently associated with ACOS, while IL-6 was independently associated with airflow obstruction and cardiovascular disease, suggesting that it may be involved in these two processes and, therefore, be an independent treatment target [44].

There have been attempts to identify genetic markers of ACOS. A recent study identified three novel loci as potentially common genetic factors between asthma and COPD; however, none of them reached genome-wide significance. These findings could suggest either that there is no common genetic component between both diseases, or that environmental factors may have concealed the genetic contribution [45]. Interestingly, genetic analysis of the COPDGene cohort identified single-nucleotide polymorphisms in the GPR65 gene associated with ACOS in a population of smokers or ex-smokers with COPD [46]. Nonetheless, albeit promising, these techniques are not available in every centre and cannot, as yet, be used as a diagnostic tool in clinical practice.

Prevalence of ACOS

Data derived from large population studies have revealed that a high proportion of adult patients with respiratory symptoms are commonly diagnosed with more than one obstructive lung disease; this is especially the case in elderly individuals [14]. In a general Italian population, de Marco *et al.* [47] showed that the prevalence of ACOS was 1.6%, 2.1% and 4.5% in the 20–44, 45–64 and 65–84-year age groups, respectively. A similar prevalence was observed in a recent study from Korea (2.3%) [29] and in the PLATINO (Latin American Project for the Investigation of Obstructive Lung Disease) study from Latin America (1.8%) [18]. In the Hisayama study, Matsumoto *et al.* [48] observed a prevalence of ACOS of 1% in a population of 8300 people aged >40 years, using COPD diagnosis with variable airflow limitation as a diagnostic criterion for ACOS.

More interesting is the prevalence of ACOS observed among populations of patients diagnosed with COPD. This prevalence can be estimated from research databases or clinical studies. The prevalence of ACOS derived from clinical studies is usually lower compared with the analysis of databases, due to the use of more restrictive diagnostic criteria. Using the Spanish consensus criteria (table 1) [11], in a cross-sectional study with 279 COPD patients, Miravitlles *et al.* [20] observed a prevalence of ACOS of 5%. In a retrospective observational study of 499 patients with COPD, Golpe *et al.* [21] observed a similar prevalence (5%) in smoking-related COPD patients but a higher frequency of ACOS in COPD caused by inhalation of biomass smoke (21.2%). Following modified criteria from the Spanish consensus that included a normal D_{LCO}, Izquierdo-Alonso *et al.* [7] detected a prevalence of ACOS of 12% in an observational, multicentre study performed in 331 COPD patients recruited in pulmonology outpatient services. Similar frequencies have been described in studies performed in other countries [6, 19]. In the COPDGene study, Hardin *et al.* [19] found that 13% of subjects with COPD also reported physician-diagnosed asthma. In epidemiological studies such as the PLATINO study performed in Latin America, a prevalence of 11.6% was described using a post-bronchodilator $FEV_1/FVC < 0.7$ and asthma diagnosis as ACOS criteria [18]. In the Spanish EPI-SCAN (Epidemiologic Study of COPD in Spain) epidemiological study, including patients with COPD and previous diagnosis of asthma before the age of 40 years, a prevalence of 17.4% of ACOS was observed among the COPD population [17].

Studies using research databases have shown a higher prevalence of ACOS because the diagnostic criteria were based on ever receiving a diagnosis of asthma in a patient with

COPD. Using these criteria, in the 2009 Korean National Health Insurance database, RHEE *et al.* [15] found up to 54.5% of ACOS among COPD patients. SORIANO *et al.* [14] showed that the frequency of ACOS in COPD increased with age, with an estimated prevalence of <10% in patients younger than 50 years and >50% in patients aged 80 years or older. In the Wellington Respiratory Survey, the estimated prevalence of ACOS was 55.2% [16]. It is clear that these percentages overestimate the real prevalence of ACOS in COPD. Elderly patients with more severe COPD are more likely to have visited more health professionals during their lives and to have ever been given a diagnosis of asthma that was registered in the medical records. This is supported by the observation that patients sharing both diagnoses (asthma and COPD) in databases have the greatest health impairment and the highest prevalence of comorbidities [49].

Treatment of ACOS

Patients with ACOS have been systematically excluded from both COPD and asthma pharmacological trials for not being "pure" subjects. As a consequence, there is no clear information about the response of these patients to most of the current pharmacological therapies. The only clinical trial performed to date in patients with ACOS studied the spirometric effects of tiotropium in 472 individuals with concomitant COPD and asthma. Improvements in lung function and a reduction in rescue medication were observed with tiotropium [50]. However, the main interest in differentiating ACOS from COPD lies in the different response to ICSs.

Some studies have demonstrated that patients with COPD and eosinophilic inflammation treated with ICSs present a significant improvement in bronchial inflammation together with a clinical and spirometric improvement, compared with those with lower blood or sputum eosinophilic count levels [51–53]. Other studies have demonstrated a significantly better response to ICSs in terms of improvement in lung function and symptoms in patients with COPD who presented higher *F*eNO concentrations, a surrogate marker of increased eosinophilic inflammation [54, 55]. In a recent *post hoc* analysis of two randomised clinical trials of salmeterol/fluticasone compared with salmeterol alone in the prevention of exacerbations, it was reported that the rate of exacerbations in patients with a positive bronchodilator test was significantly reduced when fluticasone was added to salmeterol, but this effect was not observed in those with a negative test [1]. The selective response of COPD patients with a positive bronchodilator test to ICSs has been observed for >20 years [56, 57]. Interestingly, both increased *F*eNO and increased reversibility to β_2-agonist share features of T2S and are associated with eosinophilic inflammation, which is responsive to corticosteroid treatment [37].

Two small, randomised trials with an experimental design have demonstrated that prescribing corticosteroids (oral or inhaled) according to the intensity of bronchial eosinophilic inflammation in patients with COPD was significantly superior in preventing exacerbations and improving health-related quality of life compared with the prescription of corticosteroids according to current guidelines [58, 59].

New treatments targeting the reduction of eosinophilic concentrations are being developed. Among them, the anti-IL-5 benralizumab has not been proved to reduce exacerbations in COPD patients with peripheral eosinophilia but patients with the highest eosinophilic count showed improvements in FEV1 and a reduction in the exacerbation rate, which supports further investigation [60].

In summary, patients with ACOS present three main characteristics compared with patients with COPD alone, which are interrelated: enhanced bronchial and systemic eosinophilic inflammation, increased reversibility of airflow and increased response to ICSs. These characteristics suggest that identification of ACOS in a COPD patient implies the administration of early treatment with ICSs in addition to a long-acting bronchodilator [5, 6, 8, 23, 61].

Conclusion

COPD can no longer be considered a single disease with a simple pattern of treatment. Accumulating evidence indicates that COPD is a complex disease with different expressions and phenotypes and treatment should be tailored to the patient's characteristics beyond the degree of airflow obstruction. In this regard, ACOS is a clear example of this variability [22]. ~20% of individuals with COPD may have ACOS, and ACOS patients have more dyspnoea and wheezing and present more frequent exacerbations.

The relevance of ACOS is to identify patients with COPD who may respond better to ICSs. This may be the result of young asthmatics who, despite having asthma, started to smoke and developed chronic airflow obstruction over the basis of a previous asthma component. Alternatively, some adult smokers with COPD may present eosinophilic inflammation without a known previous history of asthma. The patient in our case history had COPD with significant smoking history and $FEV_1/FVC < 0.7$ and, despite not having an established diagnosis of asthma, she had a very suggestive previous clinical history and a clearly positive bronchodilator test and a good response to steroids during exacerbations. Reliable diagnostic criteria of ACOS are needed, although initial screening can be achieved with the clinical history and lung function tests [6]. Clinical trials in this population are required to evaluate their response to available treatments.

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Chapter 6

The overlap with bronchiectasis

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David de la Rosa Carrillo[4]

Case history: A CT scan performed when evaluating a 72-year-old female COPD patient with chronic purulent sputum for a lung nodule reveals airway wall thickening and dilatation that is described by the radiologist as bronchiectasis. How does the presence of radiological bronchiectasis affect the natural history of her COPD? Would you alter her management as a result of this? Is this a phenotype of COPD or a second, separate condition?

Chapter summary: Both COPD and bronchiectasis are inflammatory airway diseases that are highly prevalent but also underdiagnosed. Apart from the fortuitous coexistence of the two diseases in some people, several studies have observed a higher prevalence than expected of bronchiectasis without any apparent cause in patients with COPD. The most important point is that COPD patients with bronchiectasis present specific clinical characteristics (greater clinical and functional severity, greater airway colonisation by PPMs and more exacerbations), which probably result in a poorer vital prognosis and a need for specific treatment. Consequently, patients with COPD and bronchiectasis may present an important clinical phenotype. Therefore, in accordance with our current knowledge of this subject, it seems reasonable to rule out the presence of bronchiectasis in patients with COPD and severe airflow obstruction, multiple exacerbations or chronic bronchial infection. Scientific research must focus on confirming the existence of any causal relationship and evaluating the most effective treatments for this special subgroup of patients with COPD.

In the pre-antibiotics era, bronchiectasis was an extremely prevalent disease with a high mortality rate, along the lines of tuberculosis [1, 2]. The healthcare improvements of the second half of the 20th century pushed it into the background, and it even came to be considered an “orphan disease” [3]. Nevertheless, we are now witnessing a growing rise in the number of diagnosed cases of bronchiectasis, possibly due to factors such as the progressively increasing longevity of the population, the chronic nature of the diseases that cause bronchiectasis, the clinical reappearance of tuberculosis and, above all, the huge improvement in image-based diagnosis brought about by the routine use of chest HRCT. However, the real prevalence of bronchiectasis is still unknown, although some recent data have thrown light on its epidemiological impact: the number of diagnoses has quadrupled in the last two decades [4, 5] and its epidemiological pattern has changed, with the elderly

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being most affected [6, 7] and an increasing number of hospitalisations and mortalities in recent years [8–10]. Earlier mortality is also evident, along with a reduced pulmonary function, a poorer quality of life and significant health costs [6, 11–15].

One of the most striking aspects of bronchiectasis is its impact, in prognostic terms, on other diseases, whether pulmonary (severe COPD [16] and asthma [17]) or systemic (*e.g.* rheumatoid arthritis [18]). Going beyond misdiagnosis, especially in those bronchiectasis patients with fixed obstruction who are categorised as COPD, the relationship between COPD and bronchiectasis has been particularly discussed in recent years because, although it is accepted that bronchiectasis has become more prevalent in patients with COPD [19–31], there are still very few reports on the consequences of this association or the existence of any possible causal relationship between the two diseases. This chapter will review the literature to date on the different types of relationship between the two diseases, as well as the impact of this relationship, therapeutic considerations in both a steady state and exacerbations, and, finally, future challenges posed by this topic.

COPD and bronchiectasis: a chance relationship?

Misdiagnosis

COPD and bronchiectasis are two chronic inflammatory airway diseases that have a high prevalence but are also both underdiagnosed [8, 32]. Although COPD is a "functional" definition, while bronchiectasis is a "radiological" definition [33], both share a similar neutrophilic inflammatory profile as well as many clinical and functional characteristics, meaning that diagnostic errors are not uncommon, especially in smokers with bronchiectasis who are classified as having COPD. This was particularly apparent in one study carried out in the UK [19], which concluded that 29% of the patients who were referred to specialists with a diagnosis of COPD from primary care were in fact patients with bronchiectasis, a disease that could in itself provide an explanation for the patients' symptoms. Moreover, the confirmation of the appearance of bronchiectasis in a tomographic study was linked to a lack of airway obstruction in some patients: a functional finding that is perfectly possible in bronchiectasis but is, by definition, impossible in COPD.

Fortuitous coexistence

The high prevalence of both diseases means that it is not uncommon to find patients who present them both at the same time, without any apparent relationship between the two. This situation causes a deterioration in pulmonary function and an overall clinical picture that is usually more marked than the deterioration resulting from either one of the diseases on its own. The most common situation may be that of a patient with COPD and a bad evolution who has suffered in the past, or is suffering at present, from diseases that cause bronchiectasis (especially post-infectious bronchiectasis), as detected in a tomographic study (figure 1). In these cases it is difficult to determine the degree of responsibility of each disease in the clinical picture and in these patients' prognosis. The diagnosis of bronchiectasis can be verified by clear, objective radiological criteria [34–36] but it is more difficult to establish the diagnosis of COPD, as this is fundamentally based on smoking habit and the presence of chronic airway obstruction [37], which are common to both diseases. Table 1 shows some characteristics of COPD patients that should provoke

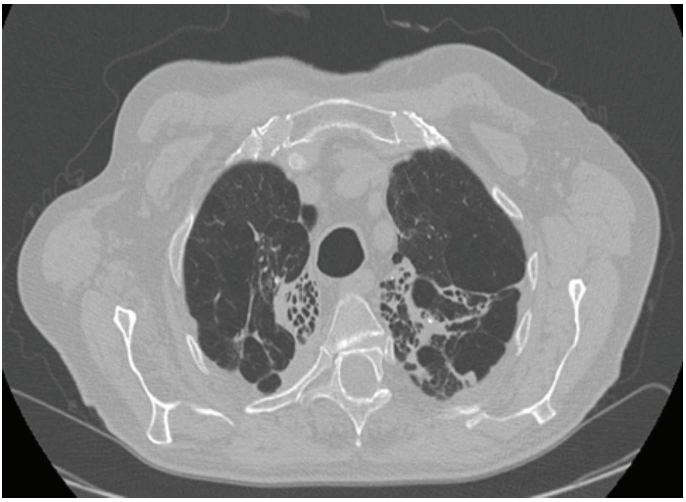

Figure 1. A patient diagnosed with COPD and post-tuberculous bronchiectasis.

suspicion of the presence of bronchiectasis, whether in association with COPD or as an alternative diagnosis.

Association between COPD and bronchiectasis

Over and above those patients with a fortuitous coexistence of both diseases, in recent years various studies have observed an almost systematic increase in the prevalence of bronchiectasis in patients with a fully verified diagnosis of COPD. As seen in table 2, the mean age of these patients is between 63 and 72 years, with a high percentage of men (between 55.6% and 99%) in contrast with other bronchiectasis series, probably because COPD is most common in men aged >60 years. Depending on which series is analysed, the prevalence of bronchiectasis varies from 2% [22] to 74% [28]. There are various reasons for this considerable disparity that need to be highlighted. First, when a study's main objective is to analyse the prevalence of bronchiectasis, this prevalence is higher because of the active search for bronchiectasis (range 35–74% *versus* 18–41%) and the inclusion of patients with

Table 1. Characteristics of patients with COPD in whom the presence of bronchiectasis must be suspected

Age <40 years
Little tobacco habit, especially in women
Sputum production >50 mL·day^{-1}
Chronic purulent expectoration
Haemoptysis
Crackles in pulmonary auscultation
Radiological suspicion (on chest radiograph), such as parallel linear densities, tram-track opacities or ring shadows
Previous history of diseases that cause bronchiectasis
Chronic rhinosinusitis
Recurrent childhood infections, particularly in the ear, nose and throat
Presence of *Pseudomonas aeruginosa* or atypical mycobacteria in respiratory secretions

Table 2. Characteristics of COPD studies with information on the prevalence of bronchiectasis

First author [ref.]	Year	Main objective	Study design	Follow-up	Patients n	Mean age years	Males %	Bronchiectasis prevalence according to COPD severity	Diagnostic criteria	Bronchiectasis type and radiological severity
O'Brien [19]	2000	Clinical and radiological features of COPD	Prospective	1996–1998	110	66.5	64	All stages: 27%; moderate-severe: 42%	Naidich [34]	Tubular: 72%; cystic: 15.5%; varicose: 12.5%
Patel [20]	2004	Correlate radiology, inflammatory markers and clinical findings	Prospective	1999–2002	54	69	NA	Moderate-severe (FEV$_1$ 38%): 50%	Smith [35] (0–24 points)	Median score: 3 (2–14); upper lobes: 29.6%; middle lobe/lingula: 29.6%; lower lobes: 66.7%
Garcia-Vidal [21]	2009	Risk factors for *Pseudomonas aeruginosa* in COPD exacerbation	Prospective	2003–2004	188	72.1	94.7	Moderate-severe: 52%	Naidich [34]	Overall bronchiectasis score[#] 11.1–22: >20%; 28–44: 20%; >44: <10%
Agustí [22]	2010	Characterisation of COPD heterogeneity	Prospective	3 years	2164	63.4	65.3	Mild: 2%; moderate: 4%; severe: 8%	NA	NA
Martínez-García [23]	2011	Factors related with bronchiectasis in COPD	Prospective	2004–2006	92	71.3	99	GOLD II–IV: 57.6%; FEV$_1$ <50%: 72.5%	Naidich [34]	Cylindrical: 90.6%; cystic: 18.9%; only lower lobes: 60.4%
Bafadhel [24]	2011	Radiological phenotypes of COPD	Prospective	15±25 months	75	67	77.3	All stages (FEV$_1$ 46%): 27%	Naidich [34]	NA
Kumar [25]	2011	Compare comorbidities and outcomes between bronchiectasis and emphysema	Retrospective	1998–2008	882	NA	NA	All stages: 35.4%	NA	Mild: 88%; cylindrical: 67%
Stewart [26]	2012	Radiological phenotypes of COPD	Retrospective	NA	3636	63.4	55.6	GOLD II: 18%; GOLD III: 24%; GOLD IV: 24%	NA	NA
Kumar [27]	2012	Correlate radiology and clinical findings	Retrospective	1998–2008	410	72	56	All stages (FEV$_1$ 52%): 69%	0–5 points	Minor: 20%; mild: 28%; moderate: 15%; severe: 8%
Brill [28]	2012	Prevalence of bronchiectasis in COPD	Prospective	NA	100	70	59	All stages (FEV$_1$ 55%): 74%	Smith [35]	Higher bronchiectasis scores in lower lobes
Martínez-García [29]	2013	Prognostic value of bronchiectasis in COPD	Prospective	2004–2007	201	70.3	90.5	Moderate-severe (FEV$_1$ 49%): 57.2%	Naidich [34]	Cylindrical: 87%; only lower lobes: 80.9%
Tulek [30]	2013	Radiological phenotypes of COPD	Prospective	2010–2012	80	68.8	95	All stages: 33.8%; moderate-severe: 40%	Bhalla [36]	NA
Gatheral [31]	2014	Determine clinical significance of radiological bronchiectasis	Retrospective	1998–2008	406	71	56	All stages (FEV$_1$ 52%): 69%	0–5 points	Minor: 40%; mild: 29%; moderate: 22%; severe: 8%

NA: not available; GOLD: Global Initiative for Chronic Obstructive Lung Disease. [#]: overall bronchiectasis score=(bronchiectasis score/bronchiectasis maximum score)×100.

previously diagnosed bronchiectasis. Secondly, the prevalence rises if HRCT is used for the diagnosis, as this method has proved to be the most trustworthy. Thus, Kumar and co-workers [25, 27] obtained varying prevalences when they retrospectively analysed the same group of patients in two different studies: 35.4% including all the patients with chest CT [25] but 69% including only those who had had HRCT [27]. Finally, the prevalence goes up when radiological criteria are used (*e.g.* those described by Naidich *et al.* [34], Smith *et al.* [35] and Bhalla *et al.* [36]), compared with studies in which they are not used (range 27–74% *versus* 2–35%). Consequently, the ECLIPSE (Evaluation of COPD to Longitudinally Identify Predictive Surrogate Endpoints) study [22], with radiological features designed to quantify emphysema with volumetric CT but no specific published criteria for diagnosing bronchiectasis, found a prevalence of bronchiectasis of merely 2–8%.

However, irrespective of the variable prevalence, there are two common elements that can be extrapolated from all these studies that endorse a real association between the two diseases. First, the prevalence of bronchiectasis increases in parallel with COPD severity and usually this prevalence exceeds that seen in the general population. Secondly, the bronchiectasis presents some special characteristics: it is cylindrical, generally occurs in the lower lung lobes (figure 2) and is not usually justified by any clear aetiology (except perhaps the natural evolution of the COPD itself, although this remains to be confirmed). All this means that bronchiectasis is difficult to diagnose with a simple chest radiograph, and thus a high degree of clinical suspicion is needed before the necessary tomographic techniques are requested.

Bronchiectasis in α_1-ATD

The relationship between COPD due to α_1-ATD and bronchiectasis deserves special mention as this is a controversial issue that has still not been clearly resolved. Some small initial series found bronchiectasis using chest HRCT in 40% of patients with α_1-ATD [38–40], and these findings were confirmed in subsequent studies [41, 42]. Parr *et al.* [42] found bronchiectasis in 70 out of 74 patients with severe α_1-ATD, 20 (27%) of whom presented clinically significant bronchiectasis. The most severe bronchiectasis was associated with the most severe emphysema, apart from one subgroup of patients with high scores of bronchiectasis and little emphysema. Other studies, however, failed to observe any relationship between bronchiectasis and α_1-ATD [43, 44]. Cuvelier *et al.* [44] did not find any greater frequency of α_1-AT alleles in patients with bronchiectasis, except for those who had both emphysema and bronchiectasis; they concluded that the bronchiectasis was probably a consequence of emphysema. It is not known whether α_1-ATD has a common pathway that contributes to the simultaneous formation of emphysema and bronchiectasis, or whether emphysema predisposes to bronchiectasis. Furthermore, the scarcity of data and longitudinal studies makes it impossible to determine whether these findings have any prognostic implications.

Is there a causal relationship between COPD and bronchiectasis?

Although COPD (and asthma) appear in many of the aetiological tables for bronchiectasis, no study to date has demonstrated any causal relationship between the two, despite the fact that the increased prevalence of bronchiectasis runs in parallel with the increase in COPD severity, and despite the suggestively similar pattern of bronchiectasis (cylindrical, lower lung lobes and unknown aetiology) usually found in patients with COPD. Therefore, the most powerful evidence currently available to endorse this possible causal relationship rests on the biological plausibility of this being the case.

Biological plausibility

Figure 3 shows a pathophysiological hypothesis that would explain a possible causal relationship between COPD and bronchiectasis. Once a PPM has infected the airways, failure to eradicate it with an antibiotic treatment or by the immune response can lead it to perpetuate itself and give rise to a chronic bronchial infection. This process is more likely to occur in patients who are more severely affected as their mucociliary defence mechanisms are more debilitated. The chronic bronchial infection unleashes a persistent bronchial inflammation and together the two progressively damage the bronchial wall with both bacterial and inflammatory proteolytic products, leading to the formation of bronchiectasis, in accordance with the classic postulates described by Cole [45] in the 1980s. The reduced activity of many antimicrobials as a result of the bronchial infection and the bronchiectasis makes it much more difficult to eradicate the PPM(s), and so both the infection and the bronchial inflammation become chronic, thereby increasing the frequency and severity of the

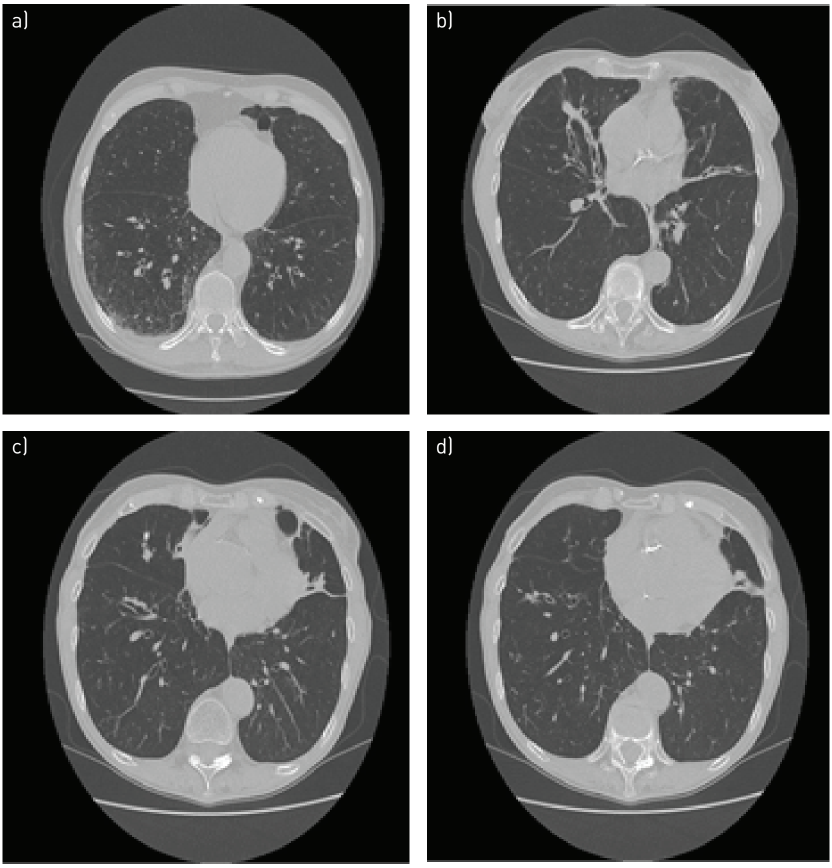

Figure 2. A patient with COPD and bronchiectasis. The three main diagnostic criteria for bronchiectasis, described by Naidich *et al.* [34], can be seen: a) signet ring sign, b) railway sign, and c) presence of bronchiectasis ⩾2 cm from the pleura. There is also d) a predominance of bronchiectasis in the lower lung lobes and large areas of emphysema associated, as well as thickening of the bronchial wall, with or without dilatation of the bronchial lumen due to bronchial inflammation.

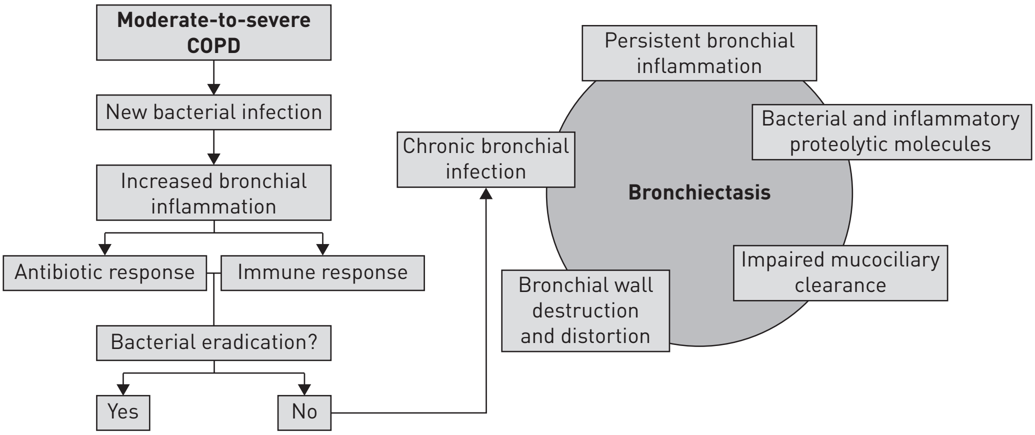
Moderate-to-severe COPD
New bacterial infection
Increased bronchial inflammation
Antibiotic response
Immune response
Bacterial eradication?
Yes
No
Chronic bronchial infection
Persistent bronchial inflammation
Bacterial and inflammatory proteolytic molecules
Bronchiectasis
Impaired mucociliary clearance
Bronchial wall destruction and distortion

Figure 3. Pathophysiological hypothesis that would explain a possible causal relationship between (moderate-to-severe) COPD and bronchiectasis.

exacerbations in a patient with COPD. This pathophysiological mechanism would explain the association between the presence of bronchiectasis in patients with COPD and the greater number and severity of the exacerbations in patients with both diseases [20, 21]. Patients with COPD and bronchiectasis would have more infection and inflammation than patients with COPD without bronchiectasis, and thus a greater possibility of more frequently crossing the symptoms threshold that defines a new exacerbation in a COPD patient [46].

Pseudomonas aeruginosa, COPD and bronchiectasis

Special attention should be given to the colonisation or chronic bronchial infection by *Pseudomonas aeruginosa* in COPD and bronchiectasis patients. Its significance may be uncertain in patients with COPD without bronchiectasis (although the literature increasingly points towards a worsened prognosis), but in patients with bronchiectasis (with or without COPD) its presence definitely results in a poorer prognosis. Accordingly, *P. aeruginosa* isolates in patients with COPD have been related to various factors, such as a greater number and severity of exacerbations [21, 47, 48], greater airflow obstruction [49], recent hospitalisations [9], more severe state according to the BODE index [21], a need for mechanical ventilation [50], frequent intake of antibiotics [51, 52] and consumption of steroids in the months prior to its isolation [53] and greater extension of the bronchiectasis [54]. Furthermore, several studies have demonstrated that chronic bronchial infection by *P. aeruginosa* is also a sign of a poor prognosis in patients with bronchiectasis, as it is associated with an accelerated deterioration of lung function [12, 55], worse quality of life [13], a greater number of pulmonary lobes affected [56], a greater number and severity of exacerbations [57, 58] and even an increase in mortality [58–60]. Nevertheless, it is still not clear whether *P. aeruginosa* itself worsens the prognosis of patients with bronchiectasis or whether it is just a marker of the poor prognosis found in patients with more severe bronchiectasis.

Impact of bronchiectasis on COPD patients

Although it is almost unanimously agreed that there has been an unexpected increase in bronchiectasis in patients with COPD, there is much less information available about the impact that one disease could have on another, and more particularly that of bronchiectasis on COPD. Some authors have demonstrated that the presence of COPD in patients with a primary diagnosis of bronchiectasis produces a significant increase in mortality from bronchiectasis, with respect to other aetiologies. Thus, Goeminne *et al.* [12], in a recent study on 245 patients with non-CF bronchiectasis, with a mean follow-up of 5.18 years and a mortality of 22%, observed that the presence of COPD significantly increased the risk of death by 2.12 (55% of deaths), generally due to respiratory causes. Similarly, a series analysed by Keistinen *et al.* [11] found that the presence of COPD increased, by 1.31 times, the risk of death in patients with bronchiectasis.

There is more information available about the relationship between COPD and bronchiectasis in the opposite direction. Thus, in patients with COPD, the presence of bronchiectasis has been related to a greater probability of suffering from pneumonia [61] and of more prolonged stays in hospitals [20] and intensive care units [62]. The study that has probably examined in the greatest depth the impact of the presence of bronchiectasis on the vital prognosis of patients with COPD was one published in 2013 by Martínez-García *et al.* [29]. 201 patients with moderate-to-severe COPD were included in the study and followed up for a mean of 48 months, during which time 51 patients died. All the patients underwent an HRCT study and a prevalence of bronchiectasis of 57.2% was found. In a univariate analysis, the presence of bronchiectasis was associated with a more advanced form of COPD, with greater systemic inflammation, poorer pulmonary function, more production and purulence of sputum and a greater number of exacerbations, as well as more time since onset of symptoms. In the multivariate analysis, the presence of bronchiectasis was significantly associated with an increased risk of death (hazard ratio 2.54, 95% CI 1.16–5.56; p=0.02), irrespective of confounding variables such as pulmonary function, age, clinical history, BMI and the presence of comorbidities (Charlson index). This relationship was maintained even when the BODE or BODEx were used as confounding variables or when the Bhalla index was used to measure bronchiectasis severity (this index also provides information on the presence of bronchiectasis, on its extension and on other findings related to its presence in the HRCT). Finally, there was a moderate correlation between the number of exacerbations, the presence of PPM in the sputum and the Bhalla index.

Treating a patient with COPD and bronchiectasis

One of the key points to take into account when making an early evaluation of the possible existence of bronchiectasis in patients with COPD is that this type of patient could need special treatment. There are two main premises for this: first, the coexistence of the two diseases means that both have to be treated, particularly at one of their most characteristic overlaps, *i.e.* chronic bronchial infection by PPM; and, secondly, there are inconsistencies in the efficacy or available scientific evidence as regards the different treatments usually used in each disease, as indicated by the relevant international guidelines [36, 63, 64]. In this respect, some treatments, such as short- and long-acting bronchodilators, theophylline, inhaled steroids and phosphodiesterase-4 inhibitors, have demonstrated a greater or lesser degree of efficacy in patients with COPD [37]. These are not always applicable, however, to patients with bronchiectasis, where there is either little scientific evidence or where some of these treatments (*e.g.* inhaled steroids) could even be harmful, even though they are widely used [63, 64]. In contrast, treatments such as long-term antibiotics (particularly when inhaled [65]), pharmacological and non-pharmacological airway clearance strategies [66] and macrolides [67–69] have so far shown greater efficacy in patients with bronchiectasis than in those with COPD. In the absence of specific studies that demonstrate the efficacy of different treatments in those patients with both COPD and bronchiectasis, the most logical indication would be the earliest possible treatment of both diseases, particularly in clinically active patients with chronic bronchial infection/colonisation by PPMs, especially *P. aeruginosa* and/or with several exacerbations [63, 64].

Treatment in the clinically stable phase

Perhaps the key question relating to treatment in the clinically stable phase is as follows: in the case of a patient with stable COPD, what additional treatment could be beneficial, and under what circumstances, and what treatments should be used with greater caution? Bronchodilators, whether β-adrenergic or anti-cholinergic, do not seem to pose a problem because of their great efficacy and safety in patients with COPD, although they have barely been studied in patients with bronchiectasis. However, ICS, characterised by their immunosuppressive effect, must be used with care in patients with COPD and bronchiectasis, who will probably present a chronic bronchial colonisation by PPM. In contrast, a patient with COPD and bronchiectasis may particularly benefit from long-term treatment with macrolides at immunomodulatory doses. Also of interest is long-term treatment with antibiotics, especially when inhaled. The prevention of exacerbations with long-term antibiotic treatment has barely been investigated in patients with COPD. Only one study has demonstrated any reduction in exacerbations (particularly in patients with chronic purulent expectoration) by using six courses of 400 mg once a day for 5 days every 8 weeks of oral moxifloxacin [70], although this assumes that these patients did not present bronchiectasis and therefore had a low probability of chronic colonisation by *P. aeruginosa*, as this microorganism is resistant to moxifloxacin. As regards bronchiectasis, the long-term use of prophylactic antibiotics is recommended [63, 64], especially in patients with multiple exacerbations and chronic bronchial infection by *P. aeruginosa*, so this profile of patients with COPD could well benefit from this treatment, although clinical studies are needed to confirm its efficacy.

Treatment for exacerbations

Very little has been published about the ideal treatment for exacerbations in patients with bronchiectasis, in contrast with those with COPD. One logical approach would be to generally treat an exacerbation of COPD with bronchodilators and systemic steroids, and to take special care when introducing an antibiotic treatment. If bronchiectasis is present, empirical treatment should be guided by the possibility of colonisation or prior chronic bronchial infection by *P. aeruginosa*. In the event of prior isolates or a high probability of colonisation by this microorganism (previous repeated doses of antibiotics or a stay in an intensive care unit), the treatment for the exacerbation should be aimed at *P. aeruginosa*, before the reception of the results of the microbiological respiratory samples (usually sputum) that must always be requested during an exacerbation process in these cases. Owing to the structural damage and the accumulation of thick mucus, as well as some characteristics of *P. aeruginosa* (particularly the creation of biofilms), antibiotic treatment for severe exacerbations should be combined and administered intravenously, at high doses and over a long period of time; a reduction in the purulence of the sputum is probably the best indicator of the ideal duration of the treatment. A common treatment for a severe exacerbation is an antipseudomonic β-lactamic or a quinolone, plus an aminoglucoside. In cases of mild exacerbations, oral quinolone may be sufficient. If there is no suspicion or confirmation of colonisation/chronic bronchial infection by *P. aeruginosa*, it is very probable that the microorganisms causing the exacerbations are those most frequently isolated in COPD patients (*Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis*), so a treatment similar to one for an exacerbation of COPD could be introduced [63, 64].

Future challenges

Although the relationship between COPD and bronchiectasis is significant because of its possible therapeutic and prognostic implications, the scientific evidence available to date is scarce. The most common finding in all the studies undertaken is probably the high prevalence of bronchiectasis with a characteristic appearance (cylindrical, in the lower lung lobes and with unknown aetiology), but there is a wide range of prevalence due to the disparity in the methodologies used. Future studies are therefore required, with a large number of patients with homogeneously classified COPD, to calculate the true prevalence of bronchiectasis in COPD. In order to obtain trustworthy data, these studies should share a series of common characteristics: a primary objective of the calculation of the prevalence of bronchiectasis; the use of HRCT; and the application of a single, validated criterion for the diagnosis of bronchiectasis and its extension, evaluated by independent radiologists with experience in this disorder.

It could also be important to examine the possible causal relationship between COPD and bronchiectasis by carrying out repeated CT under the auspices of large-scale epidemiological studies on COPD. One approach would be to consider the presence of bronchiectasis not observed previously and without any other inter-current diseases that could cause it. Today's image-based techniques make it possible to apply the same CT slices on the same sites years afterwards. It is also important to evaluate the pathophysiological routes shared by the two diseases, and the roles of the bacterial load and of exacerbations in this process, paying special attention to characteristic changes in the microbiota and their implications [71–73].

We also need to confirm whether the presence of bronchiectasis worsens these patients' prognosis and to evaluate the efficacy of different treatments (macrolides, antibiotics and mucolytics). More specifically, studies are needed to assess the impact of antibiotics (whether prescribed for exacerbations or for steady-state situations) on the microbiome of COPD patients and whether the chronic administration of antibiotics can reduce the frequency and severity of the exacerbations.

Another particularly important point would be to evaluate specific biomarkers linking COPD and bronchiectasis, such as those associated with neutrophilic inflammation (IL-1β, IL-8, TNF-α, leukotriene B4, ICAM (intercellular adhesion molecule)-1, VCAM (vascular cell adhesion molecule)-1, selectins, integrins CD11/CD18, CD47, MMP (matrix metalloproteinase)-8 and MMP-9, neutrophilic elastases, reactive oxygen species and lipid peroxidation); pulmonary function (reduced CC-16 (club cell secretory protein 16)); severity of emphysema and bronchial wall thickening (increased adiponectin, reduced sRAGE (soluble receptor for advanced glycation end products), EPHX1 (epoxide hydrolase 1, microsomal), SERPINE1 (serpin peptidase inhibitor clade E, member 1), GSTP1 (glutathione S-transferase pi 1), transforming growth factor-β1 and α_1-AT); exacerbations and mortality (increased CRP, fibrinogen, leukocyte count, IL-6, IL-8, lectin, TAP1 and TAP2 (transporters 1 and 2, ATP-binding cassette, sub-family B), and TNF-α); cellular and systemic responses to exposure to air pollution; alterations in the lung microbiome; lung ageing, such as telomere length shortening and reduced levels of sirtuins; altered susceptibility to infections; and response to both proteases/antiproteases and antibiotics. Such biomarkers would enable us to fully define a special phenotype of patients, based on a specific genotype [74, 75].

Conclusion

The prevalence of bronchiectasis without any apparent cause is high in patients with severe COPD, and this has awoken scientific interest in this association. The most plausible pathophysiological hypothesis for a causal relationship between the two diseases rests on the premise of a chronic bronchial infection in patients with COPD that would cause inflammation and progressive destruction of the bronchial wall. The presence of bronchiectasis can be easily diagnosed with HRCT, and it may be important to detect it early, as it has been linked to a poorer prognosis and could require special therapeutic management.

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Coexistent COPD and ILD

Matthew D. Jankowich and Sharon Rounds

Case history: A 67-year-old man is referred for assessment of dyspnoea and elevated estimated pulmonary artery systolic pressures in the 50–60 mmHg range on an echocardiogram. He has already been started on sildenafil by the referring physician for presumed pulmonary arterial hypertension. He has a 50 pack-year smoking history. His pulmonary function testing shows normal spirometry and lung volumes but a severely reduced diffusion capacity for carbon monoxide. On exam, he has crackles at the lung bases and clubbing. You order a high-resolution chest CT, which shows extensive upper lobe bullous emphysema, subpleural reticular changes and honeycombing with traction bronchiectasis at the lung bases consistent with ILD. How should this patient's lung disease be classified – as COPD, idiopathic pulmonary fibrosis, or something else? Why are his lung volumes and spirometry normal despite significant parenchymal lung disease on chest imaging? What is this patient's prognosis and how should he be managed?

Chapter summary: COPD and ILD coexist in patients not infrequently due to shared risk factors, especially tobacco smoke exposure. The coexistence of these conditions can make recognition through standard physiological studies such as spirometry and lung volume testing challenging. In such patients, recognition and diagnosis relies on measurement of lung diffusion capacity and HRCT. Coexistent COPD and ILD, frequently termed combined pulmonary fibrosis and emphysema, highlights the limitations of spirometry in the diagnosis of all COPD phenotypes as well as the central role of imaging in the assessment of patients with complex lung diseases. The natural history of coexistent COPD and ILD differs to that of either of these conditions when they occur alone. Controversies in management include the role of medications for the management of pulmonary hypertension, and the effectiveness of disease-specific medications such as bronchodilators or newer antifibrotic agents in such patients.

The physiological classification of lung disease based on pulmonary function testing encourages the separation of obstructive lung disease, typified by expiratory airflow limitation on spirometry, from restrictive abnormalities, typified by a reduced vital capacity and total lung capacity but preserved expiratory flow rates. Physiological testing has become essential to the diagnosis of COPD, with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification system requiring a reduced FEV_1/FVC ratio of <0.70 on post-bronchodilator spirometry to make the diagnosis of COPD. The central role of physiological testing in the diagnosis of lung disease therefore tends to make COPD and ILD, many of which are characterised by restrictive abnormalities, mutually exclusive

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diagnoses, with mixed disorders considered from a physiological standpoint only when both obstruction (decreased FEV_1/FVC ratio) and restriction (low total lung capacity) are present on pulmonary function testing.

In contrast to COPD, chest imaging with HRCT has come to assume a central role in the everyday diagnosis of ILD, especially idiopathic pulmonary fibrosis (IPF). With the application of modern chest imaging techniques, a number of patients were found to have an overlap of radiographic lesions typical of obstructive lung disease, such as emphysema, and those typical of pulmonary fibrosis, such as reticular changes and honeycombing. Many of these patients with coexistent emphysema and ILD display normal spirometry and lung volumes, with the only physiological evidence of their advanced parenchymal lung disease being a low D_{LCO} (figure 1); this overlap of pathologies is therefore not easily recognisable or classifiable from a physiological standpoint, although the extent and characteristics of the lung disease present in these individuals is clearly evident with chest imaging.

This group of patients, to whom the label of combined pulmonary fibrosis and emphysema (CPFE) syndrome has been applied, may represent only a portion of those with coexistent COPD and ILD (figure 2), as some of these patients are likely to display characteristics more skewed towards a classic COPD or ILD phenotype. For example, some patients with IPF have small amounts of emphysema that are unlikely to be of clinical and physiological consequence [1]. However, the CPFE population is the best studied of the overlap population with coexistent COPD and ILD, and illustrates an important limitation of a purely physiological approach to diagnosis of lung disease. In particular, the fact that these patients often have evidence of extensive emphysema, a pathological hallmark of COPD, but may not meet spirometric criteria for COPD, raises questions about over-reliance on strict spirometry criteria for the diagnosis of COPD, and about the role of imaging in the COPD diagnosis.

Awareness of the frequent coexistence of COPD and ILD is important for a number of reasons. The relatively normal spirometry and lung volumes seen in CPFE may lead clinicians to undertreat lung disease in these patients [1]. For example, bronchodilator medications may not be attempted in these patients because spirometry does not indicate airflow obstruction. Some of these patients may have potentially treatable forms of ILD, which may be amenable to medical therapy if diagnosed appropriately, and the presence of emphysema can adversely affect the accurate diagnosis of ILD [2]. Certain complications, such as pulmonary hypertension and lung cancer, are common in the CPFE population

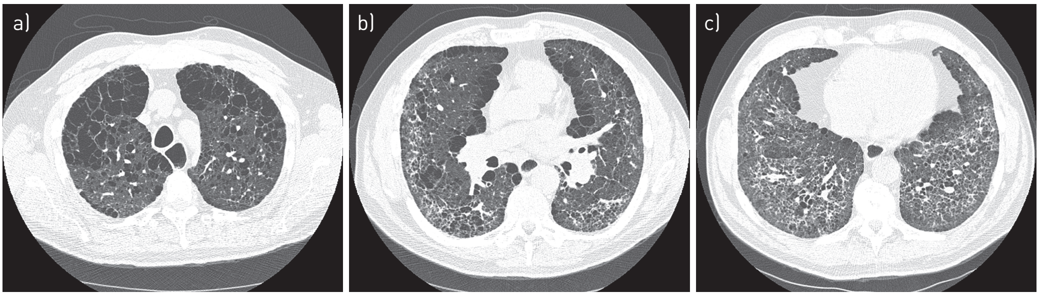

Figure 1. High-resolution chest CT images from the a) upper, b) middle and c) lower lung zones of a male former smoker with combined pulmonary fibrosis and emphysema. Note the upper lobe predominant bullous and paraseptal emphysema and the lower lobe predominant fibrotic changes. The FEV_1/FVC ratio was 0.73, FEV_1 was 81% predicted, total lung capacity was 121% pred and D_{LCO} was 18% pred.

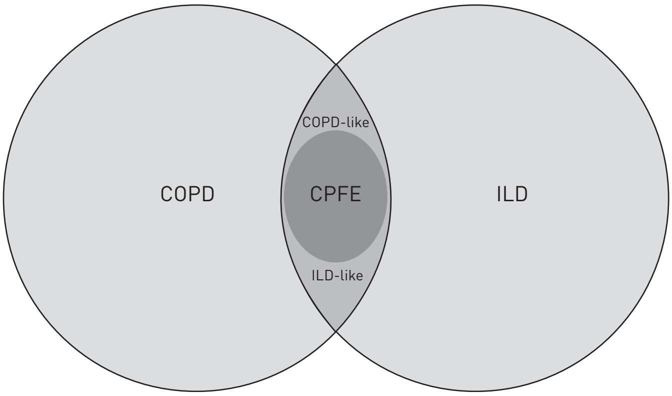

Figure 2. Venn diagram indicating the overlap between COPD and ILD. A subset of patients with overlapping disease will have typical features of combined pulmonary fibrosis and emphysema (CPFE) syndrome, while others will display predominant features of COPD (COPD-like) or ILD (ILD-like), with minor clinical or radiological features of the other disorder.

[3], and the prognosis of patients differs to patients with COPD or pulmonary fibrosis alone. In this chapter, we will discuss the epidemiology and diagnosis of coexistent COPD and ILD, risk factors, physiology, natural history and prognosis of these patients, and what is and is not known about the management of this entity.

Epidemiology

COPD and certain ILDs, including IPF [4, 5] and the smoking-related ILDs, share a common risk factor: tobacco smoke exposure. Therefore, it should not be surprising that there is an overlap between COPD and ILD. The parallels between emphysema and pulmonary fibrosis related to exposures such as smoking have been evident in pathological studies. For example, Auerbach *et al.* [6] observed that both emphysema and pulmonary fibrosis were more extensive and severe in microscopic examinations of lung specimens from smokers than from nonsmokers, and there appeared to be a dose–response relationship between both emphysema and fibrosis severity and smoking burden. However, clinical recognition of the coexistence of emphysema and pulmonary fibrosis was challenging until the advent of HRCT. CT scans have provided both a clinical means to recognise and diagnose this overlap, and have also provided data on the relationship between emphysema and ILD.

There is relatively little data on the coexistence of COPD and ILD in general population samples. Using HRCT data from the COPDGene study, Washko *et al.* [7] found that 194 out of 2416 (8%) of CT scans performed in middle-aged smokers showed evidence of interstitial lung abnormalities. Interestingly, the group of subjects with interstitial lung abnormalities had a lower median percentage of emphysema (2.2%) than subjects without interstitial lung abnormalities (4.1%) [7]. Overall, however, only 12 patients (6% of those with interstitial abnormalities, and <0.5% of the total cohort) had radiographic abnormalities so marked as to be consistent with ILD [7]. While this study demonstrated that emphysema and interstitial lung abnormalities appear to have an inverse relationship, and that an overlap of COPD and ILD is therefore expected to be uncommon, there was a low prevalence of actual ILD in this cohort.

Further data on the epidemiology of coexistent COPD and ILD in the population may come from lung cancer screening cohorts. In a cohort of 20 372 individuals who underwent screening chest CT over a 2-year period, 93 (0.46%) individuals were found to have "subclinical" CPFE [8]. 99% of these patients were men; the male predominance in CPFE has been noted previously [3]. 83% of the subclinical CPFE cohort were tobacco smokers, and while mean FEV1 and FVC were on average normal in this group, the mean *D*LCO was reduced at mean±SD 69.6±21.4% predicted. This prevalence, of approximately five out of 1000 patients undergoing screening CT, suggests that CPFE may not be uncommon in an at-risk population. Amongst patients with diagnosed lung cancer, CPFE has been reported in 5.7% [9] to 8.9% [10] of patients from two Japanese centres.

In patients with established ILD, coexistence of COPD is common. This is especially true in patients with IPF, where emphysema has been reported to be present in 18.8–50.9% of patients [3]. A recent report by CHOI *et al.* [8] found CPFE in 66 (26%) of 254 patients with biopsy-proven fibrotic idiopathic interstitial pneumonia (53 out of 66 CPFE cases with usual interstitial pneumonia on biopsy), while ANTONIOU *et al.* [11] similarly noted emphysema in 66 (35%) of 186 subjects with IPF. COPD was reported as a comorbidity in 28% of IPF cases in Olmsted County (MN, USA) [12]. Therefore, perhaps one-third of patients with IPF will have coexistent COPD or emphysema. By contrast, 2.8% of subjects with emphysema on CT scan were also found to have pulmonary fibrosis [13], so coexistent ILD will not be a common finding in patients with a diagnosis of COPD.

Emphysema may be less common in the setting of nonspecific interstitial pneumonia (NSIP) and other idiopathic pneumonias. Emphysema was noted on HRCT in 12% of cases of definite or probable idiopathic NSIP reviewed by an American Thoracic Society (ATS) working group [14]. Similarly, in a separate study by HOZUMI *et al.* [15], emphysema was present on HRCT in seven (12%) of 59 cases of idiopathic or connective tissue disease-associated NSIP, while DESAI *et al.* [16] reported emphysema in six (22%) of 27 cases of idiopathic NSIP, although only three of these had a >10% extent of emphysema. Some patients with coexistent COPD and ILD will have desquamative interstitial pneumonia or other smoking-related ILD patterns [8, 17].

In certain non-idiopathic forms of ILD, COPD/emphysema may also be prevalent. Emphysema was present in 48% of smokers with rheumatoid arthritis-associated ILD, a higher prevalence than in smoking control patients [11]. Emphysema is rarer in systemic sclerosis: four (1.8%) of 225 cases with >10% emphysema in a series by DESAI *et al.* [16]. COTTIN *et al.* [18] described CPFE in patients with a wide spectrum of connective tissue diseases, most of whom were smokers. A higher proportion of these patients were women than in other reports of CPFE. Emphysema may also coexist with other forms of ILD, such as asbestosis and hypersensitivity pneumonitis [3].

In summary, in clinically established ILD, an overlap of COPD/emphysema and pulmonary fibrosis is frequently encountered. CPFE is also not uncommonly found in lung cancer patients. Amongst ILD patients, CPFE patients are predominantly older male smokers with IPF.

Diagnosis

The symptoms of CPFE are non-specific, with prominent and progressive dyspnoea [19, 20]. The exam is usually consistent with an ILD, with basilar crackles and frequent clubbing

[19, 20]. The typical patient is a male smoker [3]. Patients with CPFE tend to have normal or only mildly abnormal spirometry and lung volume measurements [3]. By contrast, *D*LCO values tend to be markedly reduced [3], and lower than in pulmonary fibrosis patients without emphysema [1, 21] or patients with COPD alone [22, 23]. FEV1/FVC ratios are lower than in patients with pulmonary fibrosis but without emphysema [1, 21, 24, 25], probably reflecting the effects of emphysema and obstructive airways disease in these patients. However, the FEV1/FVC ratio may not meet criteria for obstructive lung disease in many cases of CPFE [23, 26]. Therefore, coexistent COPD and ILD should be suspected in a patient with suggestive findings on physical exam for ILD and relatively normal spirometry and lung volume measurements, but a low diffusion capacity.

HRCT is essential to the diagnosis of coexistent COPD and ILD [19, 20]. It allows for identification of the presence and severity of emphysema, typically predominant in the upper lobes, as well as characterisation of the pattern and extent of ILD, typically predominant in the lower lobes. Emphysema may be paraseptal or centrilobular. The most common ILD pattern present in conjunction with emphysema is a usual interstitial pneumonia pattern with subpleural reticulations, traction bronchiectasis and honeycombing, although features suggestive of other ILDs, such as ground glass, may be present. The presence of upper lobe emphysema and lower lobe ILD on HRCT is diagnostic of CPFE. A quantitative evaluation of emphysema and/or fibrosis for the diagnosis of CPFE is probably not necessary or practical in the clinical setting, although in research settings an extent of emphysema of $\geqslant$10% has been suggested to represent a level that should correlate with at least moderate COPD [1].

Risk factors

The major risk factor for coexistent COPD and ILD appears to be cigarette smoking. In a review of 607 reported cases of CPFE, 98% were current or former smokers [3]. Recent reports have supported a high prevalence of smoking in patients with CPFE [1, 22, 27]. Emphysema may develop in the setting of ILD after fewer pack-years of smoking than in smokers with or without COPD [11]. However, patients with coexistent IPF and emphysema have typically smoked more than patients with IPF alone [11, 28]. Thus, data support the concept that smoking is a risk factor for developing coexistent COPD and ILD; whether patients with ILD are generally more susceptible to emphysema development will require further study.

Most of the reported CPFE cases have been of male sex [3]. Whether this association is related to smoking behaviour or to unique biological susceptibility to this pattern of lung injury in men is uncertain. Sporadic cases of CPFE have been reported in the setting of genetic disorders known to be associated with ILD, including mutations in the telomerase gene complex [29, 30], surfactant protein C [31] and ABCA3 [32]. Of note, some of these cases with underlying genetic defects have occurred in nonsmokers. Autoimmune markers are present in some patients with this condition [20, 33, 34] and CPFE has been described in the setting of autoimmune disease [18, 35]. Like many complex diseases, CPFE probably results from an interaction between intrinsic (genetic and immune) and environmental factors (especially tobacco smoke), although the relative contribution of these factors may differ amongst patients.

Physiology

Preservation of lung volumes and expiratory flow rates is characteristic of patients with coexistent ILD and emphysema [3, 36], frequently resulting in normal or near-normal spirometry and total lung capacity in these patients. For a given severity of pulmonary fibrosis, patients with coexistent emphysema and pulmonary fibrosis have higher vital capacities than patients with pulmonary fibrosis without emphysema [1, 25]. A counterbalance of alterations in lung elastic forces in the setting of coexistent emphysema and fibrosis has been hypothesised to lead to preserved lung volumes in this setting; slow emptying of emphysematous lung units may compensate for more rapid emptying of units from fibrotic regions, and airway tethering by fibrosis may prevent the premature expiratory airway collapse typically observed in the setting of emphysema, leading to the preserved expiratory flow rates present in CPFE [3, 36, 37]. Lower respiratory system resistance has been observed on impulse oscillometry testing in CPFE compared to COPD [22, 23] or pulmonary fibrosis [22], while within-breath (inspiratory *versus* expiratory) changes in respiratory system reactance values are minimised and intermediate between values observed in either COPD or pulmonary fibrosis alone, supporting the concept of a unique counterbalancing of lung mechanics and airway collapsing forces as a result of the COPD and fibrosis overlap [22].

The severely reduced diffusion capacities seen in coexistent COPD and ILD are related to the effects of both emphysema and pulmonary fibrosis [38]. The marked reduction in diffusion capacity in these patients can be attributed to the additive effects of these diseases on the gas exchange surface area (reduced due to emphysema), alveolo-capillary membrane thickness (increased in the setting of pulmonary fibrosis), and the pulmonary circulation (destruction of the pulmonary capillary bed by both emphysema and fibrosis). Regional ventilation and perfusion matching is highly abnormal in these patients, with reduced ventilation but matched ventilation/perfusion in areas of emphysema, but high ventilation/perfusion ratios in areas of lung fibrosis [37]. As a result of these physiological alterations, hypoxaemia and pulmonary hypertension are highly prevalent in patients with CPFE [20, 28, 39]. Therefore, the coexistence of COPD and ILD produces a distinctive pathophysiology with clinical consequences.

Natural history

Lung function deterioration over time in patients with CPFE seems to be intermediate between that observed in IPF and COPD. Akagi *et al.* [40] demonstrated a smaller decline in vital capacity in CPFE relative to IPF, while Kitaguchi *et al.* [41] reported a greater decline in vital capacity in CPFE patients compared to COPD patients. Similar findings with regard to vital capacity changes have been reported by Matsuoka *et al.* [27] comparing CPFE with COPD and pulmonary fibrosis patients. Annual D_{LCO} declines are lower in CPFE than in IPF [40], but greater than in COPD [41]. However, by imaging, CPFE patients demonstrate a greater percentage increase over time in low attenuation lung areas (consistent with emphysema) compared to subjects with emphysema or pulmonary fibrosis alone [27]. This is balanced by an increase in high attenuation areas (consistent with fibrosis) in CPFE. Therefore, the magnitude of disease progression may be more apparent with imaging than with physiological measures in CPFE.

Morbidity and mortality

Patients with CPFE experience significant morbidity and mortality. Common complications of CPFE include pulmonary hypertension and lung cancer, as well as acute exacerbations and lung injury related to cancer treatments.

Pulmonary hypertension

Pulmonary hypertension is frequently present in coexistent COPD and ILD. Echocardiography has identified elevated pulmonary artery systolic pressures in over 50% of cases of CPFE [20, 28]. Pulmonary artery systolic pressures are higher in CPFE patients than in patients with pulmonary fibrosis alone [1, 28], even when there is less lung fibrosis [1], suggesting that the coexistence of emphysema and fibrosis has a synergistic effect on pulmonary arterial pressures, perhaps due to a greater restriction of the pulmonary vascular bed in this setting, as also reflected by reduced *D*LCO in CPFE. Indeed, the pulmonary artery systolic pressure is correlated with the *K*CO (*D*LCO/alveolar volume) in CPFE [20]. Elevated pulmonary artery systolic pressure identified with echocardiogram is associated with a worse prognosis [20, 24]. With right heart catheterisation, pulmonary artery hypertension is severe in CPFE, with a mean pulmonary artery pressure of 40±9 mmHg, and a mean pulmonary vascular resistance of $521 \pm 205\ \text{dyn} \cdot \text{s}^{-1} \cdot \text{cm}^{-5}$ [39]. On pathology, intimal and medial pulmonary arteriolar thickening has been described in patients with pulmonary hypertension due to CPFE, as well as a venopathy and pulmonary capillary multiplication, but plexiform lesions have not yet been reported in this setting [42, 43]. The extensive parenchymal lung disease present in CPFE clearly results in adverse effects on the pulmonary circulation, raising pulmonary vascular resistance and causing pulmonary hypertension, which in turn impacts on survival.

Lung cancer

Lung cancer has been noted frequently as a complication in patients with CPFE [3]. Lung cancer risk appears to be substantially higher in CPFE than in patients with COPD alone; however, lung cancer risk in CPFE might not be higher than in pulmonary fibrosis [44]. Lung cancer in CPFE occurs frequently in the lower lobes, in areas of fibrosis [9, 10] (figure 3). CPFE has been associated with a worse prognosis following lung cancer diagnosis than in patients with normal lung parenchyma or with emphysema [10, 45]. However, lung cancer prognosis in CPFE may be similar to that of lung cancer in ILD without emphysema [9]. Treatment options may be limited in patients with CPFE and lung cancer, and treatment-related complications, including acute lung injury (see below) are frequent [46]. Management of lung cancer is therefore challenging in this patient population.

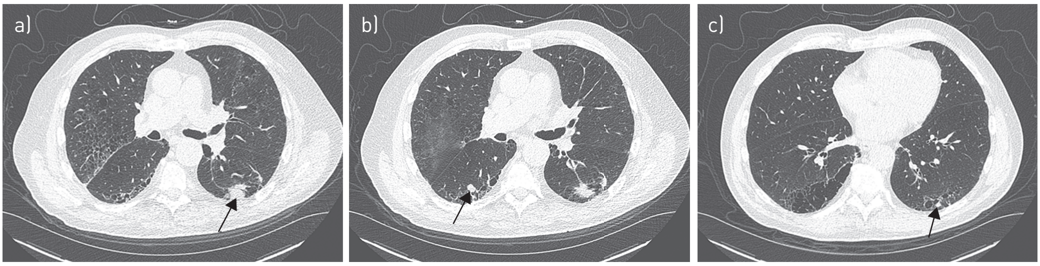

Figure 3. Lung cancer in the setting of emphysema and pulmonary fibrosis. Bilateral lung nodules (arrows) in a patient with cystic changes in the lung parenchyma. The dominant nodules in the a) left lower lobe and b) right lower lobe were squamous cell carcinomas, with c) a small focus of adenocarcinoma also noted on pathological exam. The lobectomy specimens also showed emphysema and honeycombing with fibrosis. Preoperative pulmonary function tests showed a normal FEV_1 and total lung capacity, with a *D*LCO of 66% predicted.

Acute exacerbations and lung injury

Patients with CPFE appear to be vulnerable to acute deteriorations in clinical status. Acute exacerbations, as have been observed in IPF, also occur in patients with CPFE. In one study, over a mean 2.5-year follow-up period, 24% of CPFE patients experienced an acute exacerbation [47]. As in IPF, acute exacerbations in CPFE may be fatal [24]. Higher levels of Krebs von den Lungen-6 level ($\geqslant 1050\ \mathrm{IU{\cdot}L^{-1}}$) have been shown to be a significant predictor of acute exacerbation (area under receiver operating curve of 0.7720) [47].

Patients with CPFE may develop acute lung injury after lung surgery or other cancer treatments. In a series of 10 patients who developed post-lobectomy acute respiratory distress syndrome, seven had evidence of both emphysema and interstitial fibrosis [48]. In another series, acute lung injury occurred in nine (27.3%) of 33 patients with CPFE undergoing lung resection for lung cancer [10]. Similarly, Minegishi *et al.* [9] reported that 26.9% of patients with lung cancer and CPFE experienced an acute exacerbation following surgery compared to 15.8% of patients with lung cancer and ILD but no emphysema. Acute exacerbations have also been reported following radiation therapy [9, 10, 46], chemotherapy [9, 10, 45] and even best supportive care [9, 10]. These reports suggest the importance of identifying CPFE in the pre-treatment period, and the need for heightened caution and appropriate counselling when considering treatment options for conditions like lung cancer in this patient population.

Mortality

The prognosis of patients with CPFE appears to be considerably worse than patients with COPD. Relative to subjects with emphysema alone, subjects with CPFE had significantly higher (five-fold) mortality in follow-up [13]. Relative to patients with pulmonary fibrosis but no emphysema, the prognosis of CPFE patients seems to be similar, if not worse, although reports have been variable [1, 3, 8, 24], with some indicating a better survival in CPFE [25, 49]. This variability may reflect heterogeneity in either type or severity of emphysema or ILD among these cohorts. Median survival of ⩽5 years is typical of CPFE.

A number of clinical, physiological and radiological prognostic factors have been defined in CPFE. There is a 59% higher hazard of mortality in CPFE for each unit increase in modified Medical Research Council dyspnoea score [24]. The presence of clubbing has been associated with a two-fold increase in mortality in CPFE [47]. A higher $\mathrm{FEV_1}$%/FVC % ratio (>1.2) portends a worse mortality [47], while a 10% decline in $\mathrm{FEV_1}$ over 1 year has been shown to be the best single longitudinal predictor of mortality in CPFE among pulmonary function variables [26]. An elevated pulmonary artery systolic pressure $\geqslant 30.4$ mmHg on echocardiography is associated with increased mortality risk [24]. On imaging, the presence of paraseptal emphysema [24, 49] and increased fibrosis score [8] have been associated with worse outcomes. Assessment of these prognostic markers may help in clinical decision making (regarding transplant referral, for example) in this patient population.

Assessment and management

Most data on CPFE comes from retrospective cohort studies, and randomised controlled trials are lacking in this patient population. Therefore, diagnostic and management recommendations are not based on high-level evidence. Extrapolating from findings of clinical trials in COPD or ILD may not be appropriate in this patient population, as the natural history of CPFE is different. For example in IPF, a longitudinal decline in FVC or *D*LCO is an adverse prognostic marker, while in CPFE, a decline in FEV1 is superior to FVC or *D*LCO in predicting mortality [26].

The first step in the assessment of coexistent COPD and ILD is the establishment of an accurate diagnosis. CPFE should be considered in the differential diagnosis when assessing patients, especially middle-aged or older male smokers, with: a severely reduced *D*LCO; significant dyspnoea but relatively normal or minimally abnormal spirometry and lung volumes; or significantly elevated pulmonary artery systolic pressures on echocardiography or pulmonary hypertension on pulmonary artery catheterisation. In such patients, chest imaging with HRCT should be strongly considered as part of the diagnostic work-up, especially if there are clinical signs of ILD such as basilar crackles or clubbing. When assessing patients with known or suspected ILD, the HRCT should be carefully reviewed with regards to presence of emphysema, which may not always be well reported or may be confused with honeycombing by inexperienced radiologists. Early CPFE findings may be incidentally present on lung cancer screening CTs, so these scans should be carefully reviewed for parenchymal lung disease when available, especially if there is a suspicious nodule or mass. However, low-dose chest CTs may not provide the resolution necessary for precise diagnosis. Not all patients with coexistent COPD and ILD will have a usual interstitial pneumonia pattern on HRCT, and in cases with atypical findings, such as widespread ground glass changes, appropriate work-up with serologies, bronchoalveolar lavage and potentially lung biopsy, should be carried out.

When CPFE is determined to be present, the evaluation should include a standardised assessment of dyspnoea with the modified Medical Research Council dyspnoea scale. The physical exam should note the presence or absence of clubbing and any findings suggestive of right heart failure. Pulse oximetry should be performed to assess for hypoxaemia at rest and with exertion. An assessment of functional capacity with a 6MWT is reasonable. Echocardiography should be performed to assess for elevated pulmonary artery systolic pressures, which are associated with a worse prognosis. Right heart catheterisation should be considered, especially if there is any suspicion of comorbid heart disease that could lead to elevated pulmonary capillary wedge pressure and contribute to dyspnoea or heart failure.

Smoking cessation should be aggressively supported. Given that hypoxaemia may contribute to elevations in pulmonary vascular resistance and pulmonary artery pressures, prescription of supplemental oxygen for patients with documented hypoxaemia is a standard intervention, although again there is no specific evidence of an improvement in mortality with oxygen therapy in the CPFE population. COPD-specific therapies are noted to be prescribed to only about half of patients with CPFE, even though the clinical diagnosis of COPD is applied to many of these patients [1]. We believe a trial of COPD-specific medication is reasonable in this population with significant emphysema, with follow-up of symptoms and dyspnoea scores.

There is little data on the use of anti-fibrotic medications in the CPFE population. Patients with an FEV1/FVC ratio <0.8 or a history of COPD were excluded from the ASCEND (A Study of Cardiovascular Events in Diabetes) study of pirfenidone [50], and obstructive airways disease was an exclusion criterion of the earlier CAPACITY (Clinical studies Addressing Pirfenidone in idiopathic pulmonary fibrosis: Research of efficacy and safety outcomes) studies [51]. Therefore, patients with coexistent COPD were unlikely to have been enrolled in significant numbers in these studies. Whether such patients were included in the nintedanib INPULSIS trials is unclear [52]. In a small observational retrospective cohort study including 11 patients with CPFE, 27% of CPFE patients had disease progression ($\geqslant$10% decline in FVC or $\geqslant$15% decline in D_{LCO}) on pirfenidone compared to 24% of IPF patients without emphysema [53]. Postmarketing surveillance studies may be helpful in assessing use of antifibrotic agents in patients with coexistent COPD and IPF.

Use of pulmonary vasodilators to treat pulmonary hypertension in CPFE is limited to case reports [42, 43, 54] and small case series [39], with no clear evidence of consistent efficacy. Therefore, caution should be exercised in the use of these medications. If a trial of pulmonary vasodilators is undertaken, careful follow-up of objective measures such as 6MWD or haemodynamics should be considered.

As many patients with CPFE would qualify for lung cancer screening with low-dose CT based on their smoking histories, the topic of screening should be discussed with patients. Patients with advanced disease may not benefit from diagnosis and treatment of an early stage lung cancer, and may have an elevated risk of potential harm from treatment. A discussion of lung transplantation should also be undertaken with potentially eligible patients. Palliative care referral should be considered in patients with severe or worsening dyspnoea.

Conclusion

Coexistent COPD and ILD will be encountered by physicians involved in the care of patients with ILD, pulmonary hypertension and lung cancer. An accurate diagnosis requires HRCT. There is accumulating data on the unique physiology and natural history of this condition. However, evidence-based guidance on disease management is lacking, and with the accelerating availability of new drugs to treat COPD, pulmonary fibrosis and pulmonary hypertension, questions about whether and how to apply to apply these treatments to this patient population will accumulate.

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The value of CT scanning

Samuel Y. Ash and George R. Washko

Case history: A 72-year-old man with severe COPD is referred to a pulmonary clinic for further evaluation. After a long discussion of his history, including extensive smoking as well as multiple admissions for COPD exacerbations over the past 5 years, the conversation turns to the question of CT screening for lung cancer. The patient is interested in having a CT but only if it will provide more information applicable to his immediate COPD treatment, as he is less interested in cancer screening alone. He asks his pulmonologist for his/her recommendation in this regard.

Chapter summary: Advancements in CT imaging as well as the increased availability of CT images, thanks to their proliferation in routine medical care, present opportunities for the use of CT in the management of COPD patients. These opportunities not only include more long-standing areas, such as the use of densitometry, but emerging areas, such as quantitative analysis of more distal airways and pulmonary vasculature. The overlap with lung cancer screening also raises yet more challenges and opportunities for the secondary use of huge volumes of CT data acquired for other indications.

COPD is a complex aggregate of manifestations and comorbidities that belies the simplicity of the bedside metrics we use to characterise its severity [1, 2]. CT is increasingly being exploited for its potential to better understand the pathophysiology of airflow obstruction and to identify more homogenous subsets of patients [3]. This chapter provides a detailed review of the progress and controversies of CT scanning in COPD with an eye towards where CT scanning may provide clinical benefit both now and in the future of more personalised medicine.

Densitometry

The first revelations of the potential of CT scanning for respiratory disease came in the 1980s with the introduction of densitometry [4, 5]. A CT scan provides an exquisite *in vivo* assessment of organ structure based upon tissue density and its ability to absorb photons. Tissues that appear “brighter” on a CT scan are denser and allow the passage of fewer photons from source to detector in the CT gantry, while less dense regions, such as those found in emphysema, are “darker”. Nestor Müller and colleagues quantitatively leveraged these data and introduced the term “densitometry” to assess emphysema in smokers; they

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found a highly significant association between CT measures of pathological low attenuation and those obtained on necropsy (figure 1) [5]. Specially designed software isolates the lung from the surrounding chest wall and generates a histogram distribution of voxel densities expressed in Hounsfield Units (HU). This histogram is then dichotomised based on a HU threshold that delineates pathologically low attenuating structures representing emphysema from the non-emphysematous parenchyma. The region of diseased lung tissue can then be expressed as a fraction or a percent of total.

A multitude of studies have since leveraged this technique for clinical, epidemiological and genetic investigation. The biomedical community is also critically examining its potential as a proxy for emphysema progression in trials of new pharmaceutical therapies [6]. However, major challenges exist with regard to reproducibility of the images; this is due to scan-to-scan variability in inspiratory effort and the rapid pace at which CT scanners continue to be replaced and upgraded in hospital systems [7]. While these factors are surmountable in biomedical research, we must ask whether there is clinical significance to the assessment and potential quantification of emphysema on CT scan. The best place to begin to contemplate such a question is in the literature regarding surgical lung volume reduction.

The National Emphysema Treatment Trial (NETT) was a randomised trial of surgical lung volume reduction or optimal medical therapy for patients with expiratory airflow obstruction, severe emphysema on CT scan, and hyperinflation [8]. At total of 1218 subjects were enrolled, with 608 randomised to surgery. There was no overall mortality benefit of lung volume reduction surgery (LVRS); however, subjects with upper lobe-predominant emphysema and low exercise capacity (assessed according to 6MWD) tended to live longer than their medically treated matched counterparts (figure 2). These results demonstrated a clear contribution of CT scanning to clinical care, as CT was used to characterise the distribution of emphysema as either upper lobe predominant or non-upper lobe predominant, the latter including diffuse emphysema, lower lobe disease and disease primarily affecting the superior

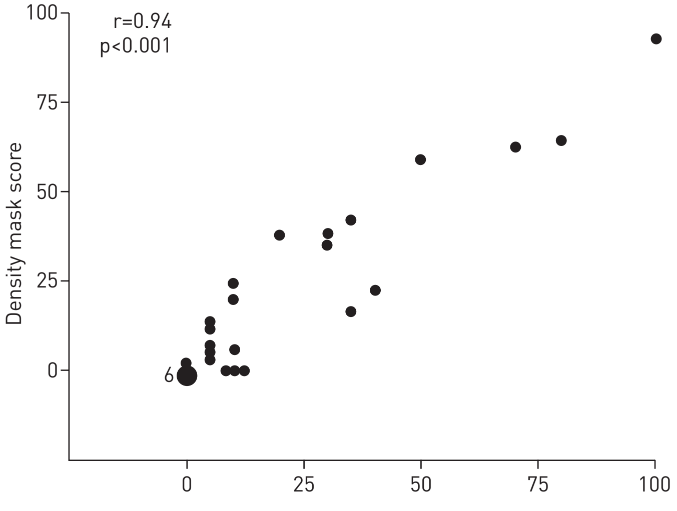

Figure 1. The lung density on CT measured using the density mask score and the degree of emphysema measured using the pathological score are highly correlated. Reproduced and modified from [5] with permission from the publisher.

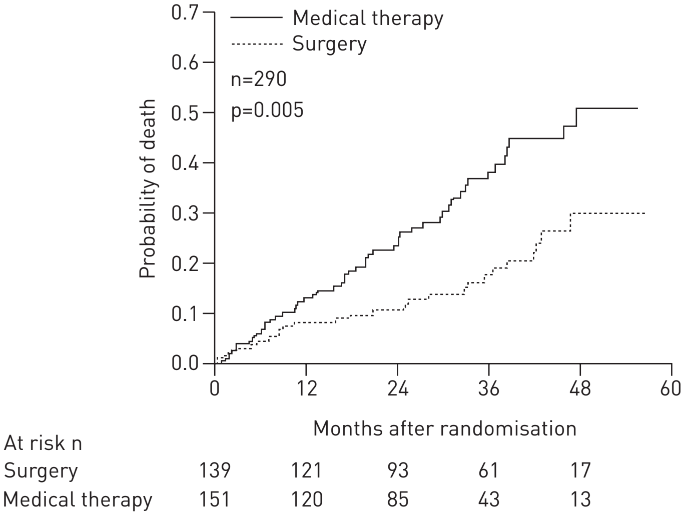

Figure 2. The National Emphysema Treatment Trial (NETT) demonstrated that in patients with low exercise tolerance and upper lobe-predominant emphysema, lung volume reduction surgery results in a significant survival benefit over optimal medical therapy. Reproduced and modified from [8] with permission from the publisher.

segments of the lower lobe [8]. Thus, in patients with severe COPD, the burden and distribution of emphysema can be used to identify patients who may experience the greatest benefit from LVRS. More importantly, the same CT findings may be used to mitigate procedural risk by advising select patients against such an invasive procedure.

The ongoing investigation and growth of bronchoscopic lung volume reduction procedures builds upon this experience and reinforces the importance of CT scanning in candidates for these procedures. For example, in the Endobronchial Valve for Emphysema Palliation (VENT) trial, CT was not only used to identify the lobe with the highest percentage of emphysema, as defined by the proportion of pixels of <−910 HU, but also to identify fissure integrity [9]. The latter has been shown to be important in bronchoscopic lung volume reduction as incomplete fissures may reduce the beneficial effect of the lobar isolation sought in certain forms of endobronchial lung volume reduction [10].

Airway analysis

A second structure in the lung that has been of keen interest to the research community is the airways. We believe that the site of expiratory airflow obstruction in smokers with COPD is the distal small airways [11]. These airways are beyond the resolution of clinical CT scanning protocols but studies have demonstrated a correlation between central airway morphology (third, fourth or fifth branching generation) and distal mural remodelling on histopathological evaluation (figure 3) [12]. Several investigations have demonstrated that subjects with a greater ratio of lumen to wall area expressed as a percentage (WA%: wall area/(wall area+lumen area) have a greater expiratory airflow obstruction and a lower FEV_1 [13, 14]. A more recent study has also demonstrated that the thickness of the central airway wall is directly associated with the historical frequency of self-reported AECOPD [15].

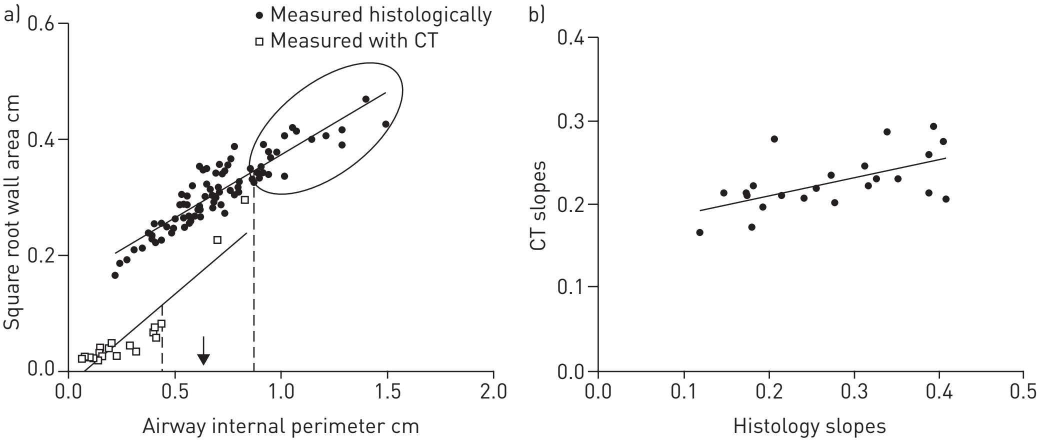

Figure 3. CT measurements of airway wall area and internal perimeter have been shown to correlate with histological airway size. While the actual CT measurements themselves result in overestimation of the histological airway size (a), there is significant correlation between slopes of the CT and histological measurements (b). a) The long dashed line indicates the internal perimeter cut-off that was used for CT (0.75 cm). The mean wall area percentage for all airways more than this threshold (encircled by a solid line) was compared with the histological measurement of the airway wall area at an internal perimeter of 4 mm (short dashed line). An arrow references the point at which the airways are at a diameter of 2 mm. Reproduced and modified from [12] with permission from the publisher.

These results provide an exciting demonstration of how CT may be used on a population basis to identify subjects with disease or those who are potentially at the greatest risk of clinically relevant events; however, there are challenges to the clinical translation of such observations. Unfortunately, a population-based predictive model is poorly predictive of outcome for a given individual. In particular, with regard to CT measurements of airways, it has been questioned whether central WA% or airway wall thickness provide enough data on which to base decisions regarding therapeutic intervention. It could be speculated that a patient with severe diffuse emphysema on CT accompanied by commensurate loss of the central airways [16] would be a poor candidate for many of the currently inhaled bronchodilating medications in smokers. While there are statistically significant associations between spirometric responses to inhaled bronchodilators and central airway wall morphology [17], there is little published data to suggest that current CT measures of emphysema or airway morphology facilitate tailored therapy of inhaled medications. Perhaps we only need to validate the available radiological measures of airway disease with regard to response to treatment. However, it is also possible that we have misinterpreted radiological measures of central airway morphology. These measures may tell us more about intrinsic airway structure and the mechanical behaviour of the airway in an elastic lung matrix than the small airway disease that is associated with chronic tobacco smoke exposure [18, 19]. For now, CT evaluation of airways therefore remains investigational for the most part and not yet of utility in day-to-day clinical practice.

Bronchiectasis may be an exception to these limitations of airway morphology. Bronchiectasis is characterised by pathologically dilated airways, which are often colonised by pathogenic microorganisms. Patients with this bronchiectasis may experience increased cough productive of mucopurulent secretions, breathlessness, frequent respiratory exacerbations and an increased risk of death (figure 4). Chronic tobacco smoke exposure is most commonly associated with a tubular form of bronchiectatic airway dilation, and its prevalence is ~50–60% in patients with moderate-to-severe COPD [20, 21].

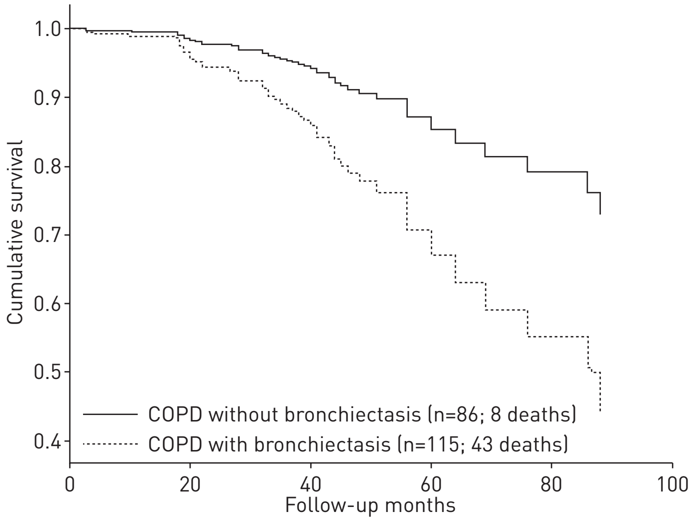

Figure 4. Patients with COPD and CT evidence of bronchiectasis have significantly worse survival compared to those with COPD but without evidence of bronchiectasis. Reproduced and modified from [20] with permission from the publisher.

In 2004, Patel *et al.* [21] reported the results of a radiological investigation of 54 subjects from the East London COPD Study. 27 (50%) of these subjects were found to have bronchiectasis on CT scan and those same 27 subjects tended to have higher levels of airway inflammatory cytokines and airway bacterial colonisation. While the presence of bronchiectasis was not predictive of the subsequent frequency of AECOPD, it was associated with prolonged recovery from such respiratory events. It is likely that the study was too small to observe an association between CT bronchiectasis and exacerbation frequency, but the presence of bronchiectasis in this and other investigations has also been associated with the isolation of respiratory pathogens, such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. Such knowledge has led to recommendations about tailored antimicrobial therapy for AECOPD based on the presence or absence of bronchiectasis in a particular patient. In addition, in 2012, Martinez-Garcia *et al.* [20] reported observations from a prospective cohort of 99 patients with COPD, 57% of whom had bronchiectasis on CT. They found that the presence of bronchiectasis on CT was associated with an increased risk of death in patients with moderate-to-severe COPD.

Further work is still required to determine the clinical relevance of radiologically diagnosed bronchiectasis. Much, if not all of the research published in this area has been based on semiquantitative visual analysis of the CT scans. Such work suffers from a lack of inter-expert reproducibility, as well as the efficiencies required for application to high throughput clinical care settings. New and exciting objective methods are currently being developed to quantify bronchiectatic airway dilation but these methods should largely be viewed as tools for clinical, epidemiological and genetic investigation.

Vasculature

It has been estimated that 30–70% of subjects with COPD have clinically significant pulmonary vascular disease [22–25]. While the observed increases in mean pulmonary artery pressure (*P*pa) tend to be mild or moderate (*P*pa ∼20 mmHg), they have also been shown to be independent predictors of increased healthcare utilisation and mortality [22–24]. Early angiographic studies reported pruning of the distal vasculature in patients with emphysema [26, 27], which, on CT scan, may manifest as a loss of distal vasculature and dilation of the main pulmonary artery.

Recently, WELLS *et al.* [28] sought to determine the clinical relevance of pulmonary arterial trunk dilation. They did so by measuring the ratio of the diameter of the pulmonary artery to the adjacent aorta (PA/A ratio) in subjects enrolled in either the COPDGene Study [29] or the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study [30]. Both were observational studies and collected CT scans of the chest as well as epidemiological and clinical data. A PA/A ratio of >1 was highly predictive of subsequent exacerbations of COPD (OR 1.86 (95% CI 1.54–2.24); p<0.001) and when limited to severe AECOPD, a PA/A ratio of >1 was associated with a greater odds of having an AECOPD than a history of AECOPD in the year prior to enrolment (OR 3.44 (95% CI 2.78–4.25) *versus* 2.01 (95% CI 1.61–2.49), respectively). While these data do not justify acquiring a CT scan simply to measure the PA/A ratio, they do nicely illustrate the information that can be obtained from imaging that is complimentary to the standard clinical practice of taking a medical history.

As previously mentioned, pulmonary vascular remodelling in smokers also manifests as intraparenchymal pruning of the distal vasculature (figure 5). In a previously published study, we hypothesised that the extent of this process that is evident on a CT scan may be

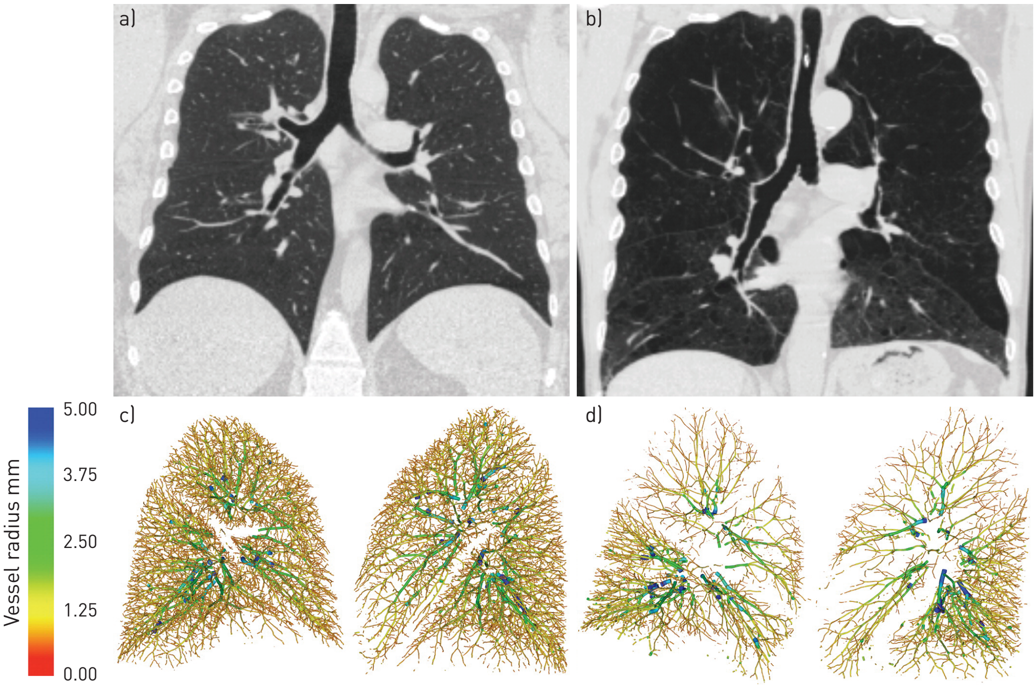

Figure 5. Coronal thoracic CT images from a) a never-smoker and b) a smoker with severe COPD with c) and d) corresponding volumetric reconstructions of the pulmonary vasculature demonstrating significant pruning of the intrapulmonary vasculature tree in the patient with COPD (d). Reproduced and modified from [31] with permission from the publisher.

directly related to the degree of clinical impairment suffered by patients with COPD [31]. Based on earlier work demonstrating the clinical relevance of aggregate vascular cross-sectional area in vessels $<5\ \text{mm}^2$, we examined the total blood volume (TBV) of the intraparenchymal vascular tree and the volume of blood vessels with a cross-sectional area $<5\ \text{mm}^2$ (BV5). We created a ratio of the two and found that reductions in BV5/TBV were associated with greater spirometric impairment, increased emphysema on CT scan and lower resting oxygen saturation. We also examined the ratio of BV5 to the nonvascular tissue volume ($\text{T}^{\text{issue}}\text{V}$) (volume of parenchyma in the lung or lobe of interest excluding blood vessels) and found that a greater ratio of distal blood vessel volume to nonvascular tissue volume ($\text{BV5}/\text{T}^{\text{issue}}\text{V}$) was associated with reductions in the single-breath *D*LCO and the 6MWD. The primary factor limiting the widespread deployment of such techniques is the technical expertise required to perform this analysis. The necessary software is increasingly available but these efforts should be thought of as research based until further validation in clinical investigation is performed.

Extrapulmonary

The preceding sections were dedicated to the pulmonary manifestations of COPD and their radiological correlates. However, COPD is a syndrome with a multitude of extrapulmonary manifestations, such as cachexia, cardiac disease and lung cancer. The following sections briefly cover the utility of CT scanning for each of these in clinical practice and biomedical research.

Cachexia

It is estimated that 25% of patients with COPD have or will suffer from the unintentional and pathological loss of skeletal muscle [32–34]. These patients will have an approximate 50% reduction in median survival [33]. There are several possible causes of this loss of muscle mass, including systemic inflammation, disuse atrophy, hormonal insufficiency, hypoxaemia and oxidative stress [35–45]. Collectively, these processes result in the cachexia observed in smokers, and it is not unexpected for many of these processes to be present in a given individual. Because of the differential loss of FFM and the reciprocal tendency for increased adiposity with age [46–50], a simple measure such as BMI may be insensitive to the loss of skeletal muscle until it is at its later stages, when it, and the underlying processes, are less amenable or even refractory to therapeutic intervention.

The challenge to clinicians and investigators is not the detection of an individual's degree of oxidative stress or systemic inflammation, but rather the detection and diagnosis of cachexia itself. This is best done by objectively assessing adipose and fat free tissues, such as skeletal muscle.

In 2002, Marquis *et al.* [51] demonstrated that a mid-thigh measure of muscular cross-sectional area on CT scan was a stronger predictor of mortality in COPD than BMI (figure 6). Further work has demonstrated that reductions in mid-thigh muscular cross-sectional area were associated with decreased 6MWT performance and increased breathlessness, even in smokers with mild COPD [52]. The thighs are not, however, routinely imaged in the context of an evaluation of respiratory disease; in a previous study, we hypothesised that novel clinical insights into COPD could be derived from quantitative assessments of structures such the pectoral muscles (figure 7) [53]. In addition to providing quantitative data on skeletal muscle bulk, chest CT also provides the opportunity to detect and objectively measure subcutaneous fat.

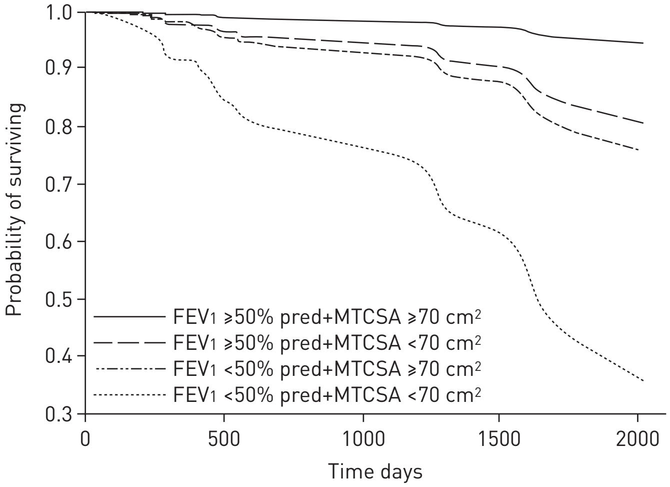

Figure 6. Survival in patients with COPD is correlated not only with FEV1 but also with the mid-thigh muscle cross-sectional area obtained using a CT scan (MTSCSA). Reproduced and modified from [51] with permission from the publisher.

In a study of 1000 COPDGene Study subjects, we previously demonstrated that pectoralis muscle bulk is statistically significantly associated with clinically relevant measures of COPD severity [53]. More specifically, the pectoralis muscle bulk within a cross-sectional area of a single axial CT slice selected just above the top of the aortic arch was inversely related to the FEV1 % predicted and highly predictive of both health status (as measured by the St George's Respiratory Questionnaire) and 6MWT. Further work is underway to determine the genetic basis of CT body composition and the prognostic value of these measures in a longitudinal investigation. The results of this ongoing work are promising but their direct clinical significance remains unclear [29]. Further work is needed to determine whether such measures can be used to help tailor regimens of PR, or whether therapeutic modification of radiological body composition alters COPD outcome.

Other markers of frailty may also be appreciated on CT scans of patients with COPD. For instance, the prevalence of osteoporosis in COPD is estimated to be 4–59%, and there are multiple factors that may make patients with COPD more susceptible to osteoporosis [54].

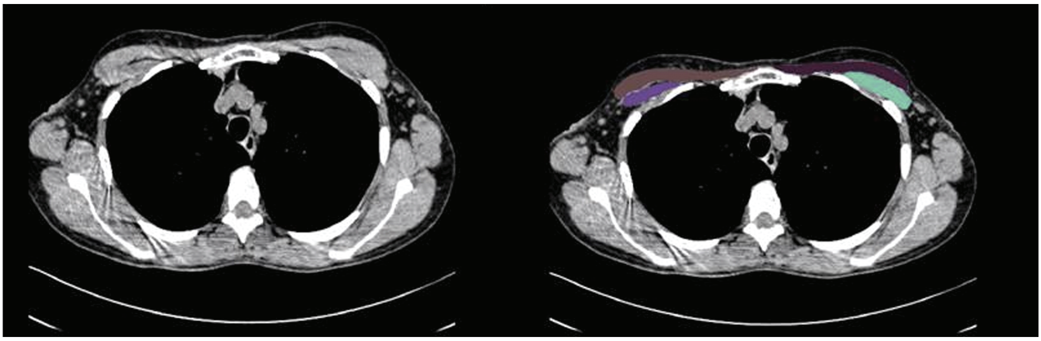

Figure 7. In patients with COPD, pectoralis muscle bulk correlates with health status and 6MWT. These sample CT scans demonstrate the appearance of the pectoralis muscles on CT (shaded in green and purple on the right). Reproduced and modified from [53] with permission from the publisher.

Thoracic CT scans have been shown to provide precise and reproducible measures of vertebral body bone mineral density, which may be useful in identifying incidental osteoporosis [55]. As with cachexia, further studies are needed to better define the role of thoracic CT in this regard.

Cardiovascular disease

Approximately 50% of subjects with COPD die from cardiovascular complications, and screening for cardiac disease may be complicated by thoracic symptoms readily attributable to respiratory disease [56–58]. Quantification of coronary and thoracic aortic calcification on dedicated cardiac CT scan has been demonstrated to be useful for the detection of previously undiagnosed cardiovascular disease [59]. A current limitation to such methods is the protocol that is used to acquire such imaging data. This typically entails a limited view of the heart with image acquisition gated to the cardiac cycle, both of which preclude its use in general respiratory medicine.

That said, a recent study by Budoff *et al.* [60] demonstrated that non-gated thoracic CT scans may provide information comparable to more focussed cardiac imaging. These investigators used data from a cohort of 50 subjects who underwent both volumetric COPDGene CT scanning and cardiac gated CT. The vascular calcification was quantified using the Agaston scoring system (sum of plaque size × plaque attenuation) and there was a very strong correlation between the two scanning methods, suggesting that non-cardiac thoracic CT scans may be used to assess cardiovascular disease.

In a subsequent study, Williams *et al.* [61] applied these techniques to the CT scans obtained in ECLIPSE. ECLIPSE was an observational study of over 2000 subjects funded by GlaxoSmithKline (Brentford, UK) to identify new biomarkers for disease progression [40]. Using these data, Williams *et al.* [61] found that the coronary calcium score (CACS) was highly predictive of poor clinical outcome. Those with a greater CACS had increased dyspnoea, a reduction in the distance walked during the 6MWT, higher levels of serum-based inflammatory biomarkers and increased mortality (figure 8) [61]. The overlap of cardiopulmonary disease in smokers may be due to common exposure and shared susceptibility to such exposure. Clearly, further work is required to understand the overlap of these conditions, but prior investigation demonstrating that cardiac medications such as beta blockers may improve respiratory outcomes in COPD, suggests that measures like the CACS could be used to guide treatment of respiratory disease [62].

Lung cancer

Lung cancer is the leading cause of cancer death in the world, causing an estimated 160 000 annual deaths in the USA alone (American Cancer Society (www.cancer.org)). Smokers, and especially smokers with COPD, are at an increased risk of developing lung cancer. The incorporation of CT scanning in disease screening has further demonstrated that the presence of emphysema is also an independent risk factor for developing lung cancer [63]. It is also clear that screening for lung cancer with CT in selected smokers may detect cancer at an earlier stage, when it is therefore more likely to be cured by therapeutic intervention.

The National Lung Screening Trial (NLST) was a lung cancer screening study of >50 000 smokers [64]. Subjects with ⩾30 pack-years of tobacco exposure were randomised to annual

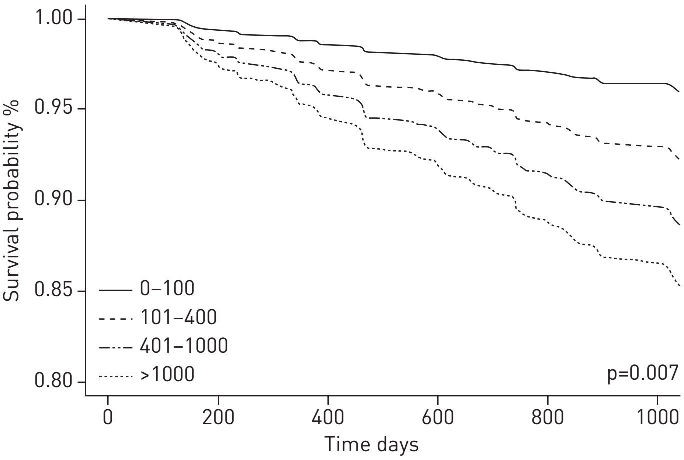

Figure 8. Analysis of the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) database demonstrated that a increased coronary artery calcium score measured on non-cardiac thoracic CT is associated with decreased survival. Reproduced and modified from [61] with permission from the publisher.

chest radiography or low-dose CT scans. CT screening detected more nodules, prompting more invasive diagnostic procedures than their chest radiograph counterparts, but the result was a 20% relative reduction in mortality. Secondary analyses are now focussed on the daunting task of identifying which smokers would best benefit from serial CT screening; recent data from the Pamplona International Early Lung Action Detection Programme (P-IELCAP) and the Pittsburgh Lung Screening Study (PLuSS) suggest that the presence of emphysema may further identify which smokers may best benefit from subsequent CT screening [65].

Radiation exposure

Much has been made of the proliferation of CT scans in modern medicine and the risks associated with such radiation exposure, and rightly so. While on the individual level the lifetime risk of death from cancer attributable to one CT scan is small, when that risk is applied across the entire population, it is estimated that as many as 1.5–2.0% of all cancers in the USA may be attributed to radiation exposure associated with CT scans [66]. Certain strategies have been put in place to try to mitigate these risks. For instance, the NLST used low-dose CT scans to try to mitigate some of this radiation exposure [67]. But while the radiation risk still remains even with low-dose CT scans, instead of suggesting that CT evaluation of, for instance, COPD should be abandoned, rather we suggest that since many of these CT scans will be obtained for other indications, we should use all of the data they provide. For example, a CT scan obtained to evaluate for possible pulmonary embolus could also be used to risk stratify a patient with COPD based on the presence or absence of bronchiectasis. Therefore, while the radiation risk associated with CT scans cannot be entirely eliminated, perhaps at least more clinical information could be used from that exposure than is currently being used.

Conclusion

For a variety of reasons, CT scans are an increasing part of healthcare delivery [66]. It is likely that the proliferation of scans will accelerate owing to the fact that Medicare and

Medicaid in the USA will now reimburse for CT scans of the chest for lung cancer screening. Thus, while we must be judicious in the use of radiation to facilitate image-based diagnostics, the chances are that in clinical practice, a significant percentage of COPD patients already have data from CT scans available. In light of this, we may not be contemplating the utility of obtaining a CT scan, but rather working to maximise the value of existing imaging data.

CT scanning will not supplant the increasing number of alternative imaging modalities under investigation for respiratory disease. MRI [68, 69], PET [70], optical coherence tomography [71] and others each have strengths that compliment the limitations of static CT imaging [72]. These may include more functional assessment of the lung or superior image resolution. Each may be viewed as a compliment to the other, and the future of biomedical imaging research lies with multimodality assessments.

With regard to CT scanning in particular, and especially as it relates to the evaluation of COPD, there has been some progress in using CT data to make clinical decisions, such as with regard to planning for lung volume reduction, risk stratification based on the presence of bronchiectasis, and screening for lung cancer. That said, while there has been significant progress in using the data that CT scans provide, there remains a wealth of untapped information within any given CT that will hopefully be useful in the treatment of COPD. Given the aforementioned likely proliferation of available CT scans, it is hoped that further efforts to identify CT scan correlates with genotypes and phenotypes in COPD will lead to findings that can be put into routine clinical practice in the near future.

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Chapter 9

Re-assessing the importance of FEV1 decline

Jørgen Vestbo[1] and Peter Lange[2,3]

Case history: An 85-year-old man is seen for COPD review and his spirometry is repeated. The FEV1 appears to have been stable over the previous 3 years. Is this compatible with COPD? How have recent data refined our knowledge on the relevance of FEV1 decline in COPD?

Chapter summary: An accelerated decline in FEV1 has for decades been regarded as the hallmark of COPD and most of our knowledge on risk factors for COPD comes from longitudinal studies examining a relationship between an exposure of interest and FEV1 decline. However, FEV1 is not a good overall measure of the processes leading to COPD and COPD progression. In particular, FEV1 decline is not a good measure of progression of emphysema. In addition, it has been very difficult to reduce FEV1 decline in intervention trials. As we learn more about factors in childhood affecting maximally attained lung function and different trajectories of FEV1 leading to COPD, we get a more balanced view of the importance of FEV1 decline.

A clinical diagnosis of COPD is usually based on the combination of relevant exposure(s), symptoms and demonstration of airflow limitation defined as a reduced ratio between FEV1 and FVC [1, 2]. Severity of COPD has often been graded using FEV1 as a percentage of the predicted value [1, 3, 4], although opponents of this easily communicable measure have argued its fallacies [5, 6]. However the degree of reduction of FEV1 is expressed, it has seemed a good measure in COPD, not just of current COPD but also as a measure of how far the disease has progressed. This notion has become very widely accepted and disseminated after the seminal study by Fletcher and co-workers [7, 8], conducted more than 30 years ago. The famous "Fletcher and Peto curve" [8], shown in figure 1, although clearly a conceptual illustration of the natural history of COPD, has shaped the way of thinking in COPD epidemiology in subsequent decades [9, 10]. It highlights an accelerated decline in FEV1 as the hallmark of COPD and provides a gold standard for measures of disease activity, as well as for testing of risk factors for COPD [10, 11].

In this chapter, we will try to provide a picture of where we are today with regard to understanding FEV1 decline, the factors associated with an excess decline, possibilities for

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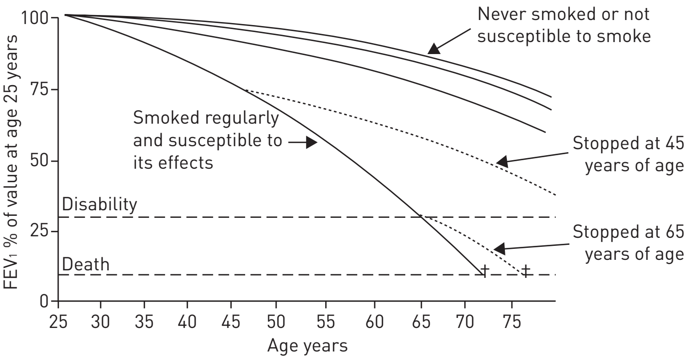

Figure 1. A conceptual illustration of the natural history of COPD, as suggested by Fletcher and Peto [8]. Reproduced from [8] with permission from the publisher.

reducing FEV1 decline, and the potential shortcoming of focusing solely on FEV1 decline as the cause of COPD.

What do we know about FEV1 decline?

FEV1 decline in health

FEV1 increases from the time it is first measured in childhood, until the age of ~20 years [12]. FEV1 grows over time in healthy children and adolescents and is affected by perinatal factors, early environmental tobacco smoke exposure, uncontrolled asthma and atopy, recurrent lower respiratory tract infections and active smoking [13–18]. It is also probably affected by biomass exposure and socioeconomic status.

After cessation of growth, there seems to be a plateau phase of ~5–10 years [12], although it has been argued that the plateau phase is the result of variability in age at cessation of FEV1 growth [19]. Subsequent decline seems almost linear when measured in absolute terms, usually as $\mathrm{mL \cdot year^{-1}}$ [20, 21], although some studies have shown decline to accelerate with ageing. Numerically, decline is larger in men than in women, with normal decline in men usually being around 25–30 $\mathrm{mL \cdot year^{-1}}$. Despite most studies having examined FEV1 decline in absolute terms, recent analyses indicate that expressing change in relative terms may actually provide advantages [22].

Risk factors for an excess FEV1 decline

Globally, the strongest risk factor by far for an excess FEV1 decline is smoking [14, 21, 23]. Smoking exposure *in utero* [13], as well as during childhood and adolescence [15], affects lung function, but the effect is best documented for FEV1 decline [9, 10, 23, 24]. Although biomass exposure is related to risk of COPD, its effect on FEV1 decline is weaker than the effect of smoking [25, 26]. The impact of occupational exposures was long a hotly debated topic but good long-term studies have documented an effect on FEV1 decline [27, 28], even in a dose–response fashion [28], as illustrated in figure 2. Asthma is a risk factor for an excess decline in lung function [29], as are airway hyperresponsiveness [30] and presence of chronic bronchitis [21, 31]. It is highly likely that pathologies underlying an excess FEV1 decline may

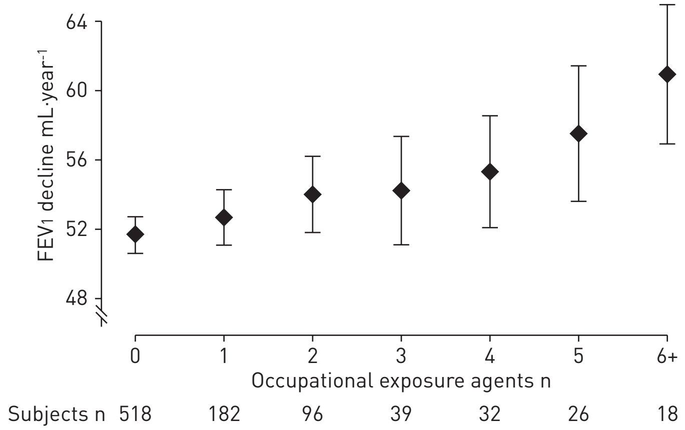

Figure 2. The effects of occupational exposures on decline in FEV1 in excess of that caused by smoking. Reproduced and modified from [28] with permission from the publisher.

vary depending on the factor or exposure causing it; thus, there is a risk in using tobacco-associated FEV1 decline as the only model for examining mechanisms of disease.

FEV1 decline in disease

We will here focus on COPD, although FEV1 decline plays a major role in other diseases, not least asthma [29, 32]. FEV1 decline in established COPD is highly variable [33–35], as expressed in figure 3. In established COPD, smoking remains a strong risk factor for an excess decline in lung function. In addition, presence of emphysema is consistently associated with a more rapid decline in FEV1 [33, 35]. In the ECLIPSE (Evaluation of COPD to Longitudinally Identify Predictive Surrogate Endpoints) study, bronchodilator reversibility was also associated with excess FEV1 decline [33], whereas it was not in patients with less airflow limitation in the Hokkaido COPD Cohort Study [35]. In the BODE cohort study and in the TORCH (Towards a Revolution in COPD Health) trial, low BMI was associated with an excess decline in FEV1,

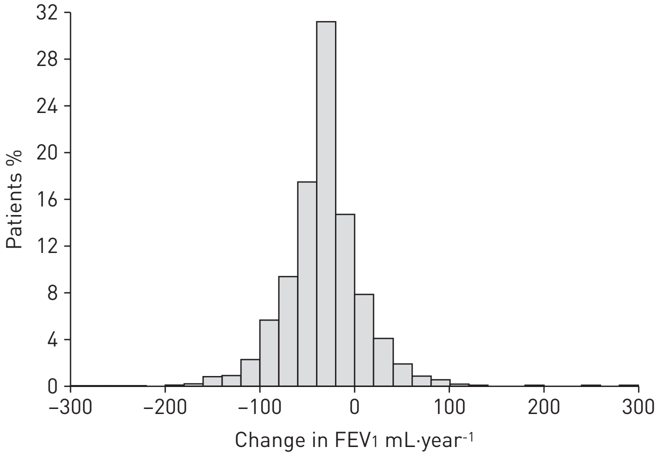

Figure 3. Distribution of estimated annual rates of change in FEV1 in the ECLIPSE (Evaluation of COPD to Longitudinally Identify Predictive Surrogate Endpoints) study. Reproduced from [33] with permission from the publisher.

possibly serving as a proxy of emphysema [34, 36]. Exacerbations also have an impact on FEV1 decline [33, 36–38], but the effect is not very large [31], indicating that different pathological processes drive FEV1 decline and risk of exacerbations.

Burrows *et al.* [39] introduced the term "horse-racing effect" to illustrate that subjects with the most rapid decline in lung function would also on average have lower lung function at any given point when comparing with others of the same age. Whereas this makes sense if it is assumed that the decline starts from a common FEV1 level in early adulthood, the "horse-racing effect" need not be valid if the maximally attained levels at which the decline starts differ substantially between individuals. In addition, in cohorts of COPD patients as opposed to healthy individuals, smoking cessation may be a result of an advanced disease and this may result in a positive correlation between low initial FEV1 level and a less steep FEV1 decline. In fact, several COPD cohort studies have shown this relationship, *i.e.* FEV1 decline is faster in patients with higher FEV1 level at baseline examination [17, 33, 34, 40]. Although we find selection bias to be the most likely explanation, it is noteworthy that analysis of FEV1 in relative instead of absolute terms (in percentage of the initial value lost per year) leads to the presence of a "horse-racing effect", whereas analyses of FEV1 decline expressed in $\text{mL} \cdot \text{year}^{-1}$ do not [22].

Biomarkers of FEV1 decline

As assessment of disease progression where the measure takes years to perform is not feasible (neither in clinical practice nor in clinical trials) [41], several biomarkers have been suggested for assessing disease activity. Burrows *et al.* [39] suggested measures of small airway function, based on findings from smaller studies, but subsequent longitudinal studies could not confirm a significant value, *e.g.* of indices from the single-breath nitrogen test [42, 43]. Markers of systemic inflammation as well as pulmonary-derived biomarkers such as surfactant proteins have been examined in patient cohorts together with measures of epithelial repair. Markers of systemic inflammation (analysed alone or in groups of biomarkers) have been shown to relate to exacerbations, hospital admissions, comorbidities and mortality [44–51], but not to FEV1 decline [33]. Blood eosinophilia was associated with less decline in FEV1 in the Hokkaido COPD Cohort Study [35] and with less risk of developing emphysema in the ECLIPSE study [52] but more data are clearly needed. Club cell secretory protein 16 is needed in epithelial repair and was the only biomarker associated with FEV1 decline in the ECLIPSE study [33]; this was replicated in a retrospective analysis of the Lung Health Study [53] but the association is very weak and unlikely to be of value in clinical practice. The main challenge for examining biomarkers in COPD relates to the likelihood of different biomarkers being of importance at different stages of the disease and their possible variation among COPD phenotypes.

Change in FEV1 decline

With FEV1 decline being seen as the hallmark of COPD and the most important measure of disease progression, a major aim of treatment has been to reduce this decline. Most commonly, treatment with ICSs has been investigated, with FEV1 decline as the main outcome measure. All initial trials failed on this outcome [54–57], although one meta-analysis showed a small impact of uncertain clinical importance [58] and another did not [59]. The UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial of the long-acting anticholinergic drug tiotropium was also clearly negative on this outcome [60], although subsequent subgroup analyses have indicated that there may be an effect in patients with mild or previously untreated disease [61, 62]. In a *post hoc* analysis of the TORCH trial, an effect of treatment with ICSs and/or a long-acting β-agonist was seen on FEV1 decline [36], but this finding requires replication. Interestingly, FEV1 decline has gradually decreased over time in these large-scale intervention trials, either indicating a different composition of patients with respect to disease origin or phenotype, a higher prevalence of smoking cessation or an effect of generally improved overall management of the disease. This of course raises the question as to whether FEV1 decline is too variable and at the same time has too little change over a realistic time-frame for this to be a relevant outcome in drug trials.

It has proven easier to show changes in FEV1 decline as a result of reduction in harmful exposures. This is the case for smoking, where findings from observational studies [7, 23, 24] have been confirmed in the Lung Health Study [63, 64]. Interestingly, reduction in biomass exposure has also been shown to reduce FEV1 decline in recent large effectiveness trials [65, 66].

The "figure 2 dilemma"

As mentioned previously, the "Fletcher and Peto curve", as shown in figure 1, has achieved almost iconic status [3]. However, in their paper from 1977, Fletcher and Peto [8] also published another figure, depicting the problem of identifying susceptible smokers in time to prevent death (figure 4). Someone at the age of 40 years with an FEV1 below the average value could either be deteriorating along a "fast decline trajectory" from an initially high FEV1 or could be experiencing a normal FEV1 decline with a smaller than average FEV1 to start out with (the "low maximally attained FEV1 trajectory") or a mixture of these two trajectories. This dilemma illustrates the need for identifying biomarkers of an excess decline in lung function.

However, combined with the variable, and often surprisingly modest, FEV1 decline in established COPD, it also indicates that a significant proportion of subjects with moderate and severe COPD may have experienced a more or less normal FEV1 decline but have had a low maximally attained FEV1 at age 25 years due to previous susceptibility and exposures.

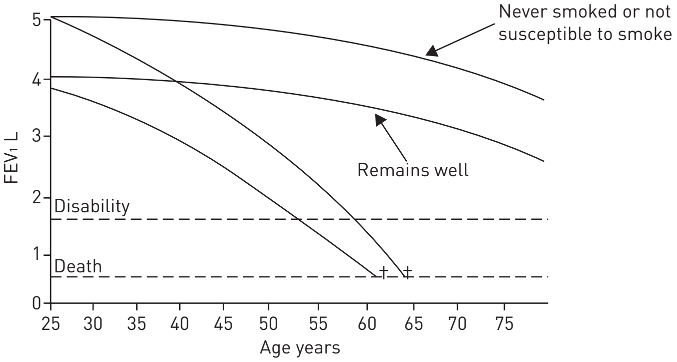

Figure 4. Illustrating the dilemma in determining whether someone at age 40 years with a height-standardised FEV1 slightly below the expected value is deteriorating in lung function with an accelerated FEV1 decline or simply following a trajectory with a suboptimal level of lung function. Reproduced and modified from [8] with permission from the publisher.

Analyses of data from the Copenhagen City Heart Study suggest that this may indeed be the case [67]. This has significant implications. First, the origins of COPD should be looked at much earlier [18, 68] and, secondly, factors that affect risk of disease progression may not be detected if FEV1 decline is used as the outcome in all-comers with COPD.

Comment

Do these shortcomings mean that FEV1 decline is of less interest for future studies of the natural history of COPD?

No: there is solid evidence behind using FEV1 decline as a measure of disease progression in COPD and as one of the ways of measuring long-term consequences of lack of control in asthma. However, FEV1 is not an overall measure of all the processes involved in disease progression and should therefore not be regarded as "the holy grail" of COPD. With our revived interest and preliminary understanding of the role of both maximally attained lung function and subsequent decline, it is clear that we desperately need biomarkers to determine whether a subject has progressive disease or is just left with the airway and parenchymal scarring from previous disease activity. Without this information, future trials of interventions with FEV1 decline as the outcome risk being seriously diluted, with the effect that efficacious interventions will be discarded.

Additionally, a reminder of the shortcomings of FEV1 decline should help us focus on other measures of disease progression. With the current interest in COPD phenotypes [69], it seems obvious that different phenotypes may have different patterns of progression and that they need to be measured differently. FEV1 decline is probably a poor measure of progression of emphysema. In the ECLIPSE study, where COPD patients were not selected with respect to their emphysema status, it was possible to measure change over 3 years and to suggest biomarkers associated with emphysema progression [52]. It is likely that other phenotypes will require other measures or, in today's jargon, precision medicine will require precision monitoring.

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Chapter 10

The use of multidimensional indices

Bartolome R. Celli[1] and Ciro Casanova Macario[2]

Case history: A 66-year-old woman with COPD attends for review. She has an FEV1 of 48% predicted, a BMI of 21 kg·m^{-2}, frequent exacerbations, exertional breathlessness when walking 100 m on the level and comorbid osteoporosis. What is the best way to predict her future mortality risk? How can multidimensional indices inform prognosis? What are the strengths and weaknesses of the available tools?

Chapter summary: Because the hallmark of COPD is the presence of airflow limitation, its severity and progression have been defined using the degree of airflow limitation. Research has shown that extrapulmonary manifestations of COPD are important and that they relate to poor outcomes. COPD is now considered to be a disease with systemic manifestations; it is therefore clear that there is a need to quantify and to incorporate the consequences of those manifestations to better reflect the actual compromise of patients. To grade disease severity, the index must not only relate to all-cause mortality, it should also reflect specific organ involvement or failure. This chapter provides a summary of the strengths and weaknesses of most of the indices available. Perhaps the time has come not to develop new ones but rather to test their practical impact on the management of patients in the clinical arena.

Although COPD is primarily characterised by airflow limitation due to chronic bronchitis, emphysema or both, a number of systemic manifestations that accompany this disease can effectively signal an increased risk for mortality [1–3]. Recognising these manifestations provides a more comprehensive assessment of disease severity and helps elucidate the prognosis. Several factors, including FEV1 [4–6], AHR [4, 7], severity of dyspnoea [8], gas exchange disturbances [9], lung hyperinflation [10, 11], pulmonary hypertension [12], malnutrition [13], impaired exercise capacity [14–16], health-related quality of life [16], anaemia [17, 18] and other comorbidities [19, 20], have been identified as individual predictors of disability and/or mortality in COPD. In this chapter, we review these variables as predictors of poor outcome and determinants of disease severity, and we discuss the ability of multidimensional tools to more broadly characterise COPD severity, assess response to therapy and exacerbations, and predict mortality.

Definition of disease severity

The definition of disease severity that we will use is as follows: variable or set of variables that provide the likelihood of death or organ failure resulting from disease progression. The

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severity should not only define the outcome of the person as a whole, but should also relate to the failure of the organ. For example, age is associated with a poor outcome (older people are more likely to die) but may not relate to failure of the lung; comorbidities certainly impact on mortality and poor health status but may not relate to the severity of lung compromise.

Predictors of outcome in COPD

Forced expiratory volume in 1 s

FEV_1 expressed as a percentage of FVC has been used as the standard measurement of airflow limitation and COPD severity since the 1800s [21, 22]. Fletcher and Peto were the first to identify a relationship between airflow obstruction and outcome [23]. The investigators found that in patients with COPD, the risk of disability was correlated with the initial FEV_1. These findings were expanded by N.R. Anthonisen and colleagues in the intermittent positive pressure breathing trial [4] and in the Lung Health trial [24], which identified both age and FEV_1 as independent predictors of mortality. A number of studies have since confirmed and further described the relationship between FEV_1, all-cause mortality and cause-specific mortality [5–9, 25]. MANNINO *et al.* [26] reported data from NHANES-1 (National health and Nutrition Examination Survey). A total of 1301 deaths were found among 5542 adults followed for 22 years in the USA. There was a higher risk of death among patients with moderate or severe COPD identified using spirometry [26]. Recently, there has been a drive to minimise the importance of FEV_1 as a valuable component of lung disease evaluation, even though FEV_1 not only predicts death but also the disease severity of the target organ.

Airway hyperresponsiveness

The importance of AHR in COPD has been studied. In the Netherlands, histamine challenge AHR was evaluated in ~2000 patients followed for 20 years. In the mortality analysis of this study, HOSPERS *et al.* [27] found that increased AHR predicted COPD mortality after adjusting for sex, age, smoking history and a number of confounders. However, the number of COPD deaths (n=21) was very small. In the Lung Health Study (LHS), TASHKIN *et al.* [28] observed an association between the response to methacoline challenge and faster lung function decline in >4000 patients with mild COPD. Most studies have used bronchial reversibility and not histamine challenge as the marker of AHR, and the results show a more rapid decline in lung function in patients with bronchial reversibility [7, 29]. However, more studies are needed to better define the relationship between AHR and mortality.

Dyspnoea

Dyspnoea is the most disabling symptom of COPD [30] and the primary reason for patients to seek medical attention [31]. The correlation of breathlessness and FEV_1 has been noted to be weak at best [32, 33]. A number of studies have identified dyspnoea as an independent predictor of mortality. In a prospective study, dyspnoea was measured using the Medical Research Council (MRC) dyspnoea scale, in a cohort of 227 COPD patients [8]. The 5-year survival rate was better predicted with dyspnoea ($p<0.001$) than with FEV_1. We also observed dyspnoea (measured using the modified MRC (mMRC) dyspnoea scale) to be an important predictor of mortality in a much larger cohort of 625 COPD patients [34].

Dyspnoea, which is easy to measure, not only relates to mortality but very importantly to the physiological compromise of the respiratory system [30, 35, 36]. It should therefore be an integral part of the evaluation of patients with COPD.

Hypoxaemia

The presence of hypoxaemia (arterial oxygen tension ($P_{\mathrm{aO_2}}$) <55 mmHg or arterial oxygen saturation <88%) has long been associated with disability and mortality in COPD [37, 38]. Its correction results in better survival [39]. Two important controlled trials provided the evidence. The MRC randomised patients to receive15 h of continuous oxygen or room air [40]. The study found a significant reduction in mortality among patients given oxygen supplementation during a follow-up period of 5 years. The Nocturnal Oxygen Therapy Trial (NOTT) compared 12 h of oxygen supplementation to 24 h of oxygen supplementation [41]. Mortality among patients given continuous oxygen for 24 h was half of that amongst patients given oxygen for only 12 h, proving that survival in hypoxaemic patients with COPD is proportional to the number of hours of oxygen supplementation. The level of oxygen in the blood is also related to the degree of lung physiology compromise [42], and therefore could be used to define COPD severity. However, obtaining arterial blood gases can be bothersome for routine practice.

Hypercapnia

Hypercapnia is frequent in advanced COPD and reflects both ventilation/perfusion inequality and decreased alveolar ventilation. The presence of chronic hypercapnia is usually associated with decreased survival in COPD [23–25, 43–46]. Hypercapnia is commonly associated with hypoxaemia and it has been difficult to elucidate which gas exchange derangement carries the most ominous prognosis. In 4552 hypoxaemic patients receiving long-term oxygen therapy (LTOT) in Japan, 1611 patients died during the follow-up period (5-year survival 39.5%) [46]. The cumulative survival curves for the hypoxaemic, hypercapnic patients were similar to those of hypoxaemic, normocapnic patients. Cox's proportional hazards models identified age, sex, $P_{\mathrm{aO_2}}$ and vital capacity % as independent predictors for survival but not arterial carbon dioxide tension ($P_{\mathrm{aCO_2}}$) or FEV1/FVC. However, other authors have found $P_{\mathrm{aCO_2}}$ to be an independent predictor of mortality [39]. Given the difficulty in dissociating simple hypercapnia from the effect of hypoxaemia, the $P_{\mathrm{aCO_2}}$ has not been very useful in helping determine disease severity in stable COPD.

Hyperinflation

Lung hyperinflation is frequent and important in COPD. It is recognised on physical exam by the barrel-shaped chest seen in patients with emphysema, and results from destruction of lung parenchyma with loss of lung elastic recoil. The inspiratory capacity (IC), which reflects the end-expiratory lung volume, shows an inverse relationship with dyspnoea during exercise in patients with COPD [36, 47, 48]. Casanova *et al.* [10] noted that the "inspiratory fraction" defined by the IC/total lung capacity (TLC) ratio at rest was an excellent predictor of survival. In 689 patients, IC/TLC was an independent predictor of mortality after 34 months of follow-up. The increase in mortality became critical for an IC/TLC ratio of <25% (critical hyperinflation). Hyperinflation is known to alter respiratory muscle anatomy and decrease its capacity to generate pressures [49], as well as affect ventricular filling [50]. Measurement of hyperinflation is a good marker of lung dysfunction, but it is difficult to determine and thus of limited use in the generation of a multidimensional index.

Pulmonary hypertension

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (Ppa) at rest of ⩾25 mmHg. Although PH is common in COPD, when present, it is usually mild to moderate in severity [51–53]. In a retrospective study of 998 patients undergoing right heart catheterisation, CHAOUAT *et al.* [51] only identified 11 patients as having severe PH as a result of COPD. They reported an increased mortality rate among these patients when compared with a control group of 30 COPD patients with no evidence of severe PH. It is generally accepted that the presence of pulmonary PH in COPD correlates with the presence of chronic hypoxaemia [54, 55]. However, studies have shown that treatment with LTOT reverses the progression of PH, although complete normalisation is infrequent. WEITZENBLUM and CHAOUAT [53] determined Ppa in three consecutive right heart catheterisations in a small group of COPD patients (mean±SD P_{aO_2} 50±6.6 mmHg). The investigators found a significant decrease in Ppa among 12 out of 16 patients (from 28±7 to 23.9±6 mmHg ($p<0.005$)) after correction of hypoxaemia. Other studies have shown that not all hypoxaemic patients respond with a decrease in Ppa after oxygen administration. In the study by ASHUTOSH *et al.* [54], the response of the Ppa to the administration of 28% oxygen for 24 h was measured among 28 patients with COPD. 17 patients responded with a decrease in Ppa of >5 mmHg and 11 did not. More importantly, the investigators found an 88% 2-year survival among responders *versus* 22% among non-responders. These findings suggest that LTOT attenuates the development of more severe PH over time. KESSLER *et al.* [55] followed 131 COPD patients with mild-to-moderate hypoxaemia who underwent two right heart catheterisations and did not meet criteria for LTOT for 6.8 years. The authors found that higher resting and exercise Ppa at baseline predicted the development of pH over a 6-year period. There is therefore no question that pulmonary vessels are affected in COPD [56]; however, the difficulty in determining pulmonary arterial hypertension in clinical practice makes this an unlikely candidate to integrate into a multidimensional index.

Malnutrition

The prevalence of low body weight in COPD is in the range of 20% and it increases to 35% among those who have more severe disease (hospitalised) [57, 58]. Several studies have found that BMI is an independent risk factor for COPD mortality [13, 59]. LANDBO *et al.* [59] found BMI to be an independent predictor of all-cause and respiratory mortality among COPD patients with an FEV1 <50% predicted. The impact of weight change on survival in COPD was also examined retrospectively by SCHOLS *et al.* [60] in 400 COPD patients participating in PR. A low BMI ($<25\ \mathrm{kg \cdot m^{-2}}$) was associated with a significant increase in the risk of mortality ($p<0.001$). Of 203 COPD patients who received nutritional support, weight gain (>2 kg over 8 weeks) was a significant predictor of survival. Studies using more complex tests to evaluate nutrition, such as mid-thigh [61] and mid-arm [62] muscle cross-sectional area obtained by CT, have also shown significant associations between malnutrition and mortality in COPD, with a predictive value that is superior to that of BMI. Because loss of muscle mass is associated with decreased respiratory muscle strength [63], decreased exercise performance [64], more advanced emphysema [65] and mortality, it is a simple test to consider for multidimensional indices.

Exercise capacity

Exercise intolerance afflicts many patients with COPD and is likely to be multifactorial, reflecting the integration of the neurological, respiratory, cardiovascular and musculoskeletal systems. The peak oxygen uptake (peak V'_{O_2}) determined during a cardiopulmonary exercise test (CPX) has been shown to predict survival in COPD patients undergoing lung resection [16, 66] and to be a better predictor of survival than FEV1 and health status [67]. In a study by Epstein *et al.* [68], COPD patients unable to perform a CPX were 11 times more likely to die following lung resection than those able to complete the test independent of the peak V'_{O_2}.

6MWD is a simple field test that has also been correlated with mortality in COPD patients in a variety of settings, including post-PR [69] and lung volume-reduction surgery (LVRS) [70, 71]. In a study by Gerardi *et al.* [69], the 6MWD was a better predictor of survival than FEV1 in patients following rehabilitation. Pinto-Plata *et al.* [14] measured 6MWD in 198 patients with severe COPD who were followed for 2 years. Survival improved progressively with increases in the 6MWD. Patients unable to walk 100 m had a mortality rate approaching 90%, while those with similar airflow limitation who walked >400 m had significantly higher survival ($p<0.0001$). The 6MWD predicted mortality better than FEV1 and BMI. Similar findings were reported by Cote *et al.* [72] in >1500 patients with all degrees of obstruction, a finding later supported by data from the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study [73]. The shuttle walk test, another field test to evaluate functional capacity in COPD, has shown the same predictive property [74]. Because field tests are easy to conduct, they are perfect candidates to include in a multidimensional index. However, there has been some resistance, given the limitations regarding the personnel, time and space needed for the test.

Health status

Health-related quality of life (HRQoL), defined as "The extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment", is an important outcome in itself [75–77]. Importantly, a weak association between HRQoL and FEV1 has long been described. Domingo-Salvany *et al.* [78] were the first to describe an association between HRQoL and mortality in 321 men with COPD followed for an average of 4.8 years. The predictive value of HRQoL has been confirmed in several studies [79, 80]. Martinez *et al.* [80] identified HRQoL as a predictor of mortality in a study of 609 patients with severe emphysema enrolled in the National Emphysema Treatment Trial (NETT). However, health status questionnaires are difficult to obtain and do not relate very well to the severity of lung dysfunction; therefore, although they are capable of predicting mortality, they do not totally fulfil the definition of determining disease severity.

Anaemia

Several reports suggest that anaemia in COPD patients may be more prevalent (10–15%) than expected and could be associated with increased mortality [17, 18, 81, 82]. In a study of 2524 COPD patients who were prescribed LTOT, 12.6% of males and 8.2% of females were identified as anaemic [83]. Recently, in a cohort of 683 COPD patients, anaemia was found in 17% of the patients in contrast to polycythaemia, which was present in only 6% of the patients (and when present, carried no clinical relevance) [17]. Anaemic patients had significantly higher dyspnoea, a lower 6MWD and a shorter median survival (49 *versus* 74 months) when compared with non-anaemic COPD patients. These differences remained significant when controlling for the relevant demographic, physiological and disease covariates. However, a relationship between anaemia and severity of COPD has not been reported. Although easy to measure, again, it may not be appropriate to include it in a multidimensional index.

Comorbidities

Tobacco use is without doubt the most important aetiological factor in the development of COPD [84]. Cigarette smoking induces a state of systemic inflammation characterised by the intense interaction and accumulation of cells capable of creating a marked oxidant–anti-oxidant imbalance and cellular injury [85, 86]. Miller *et al.* [87] reported that the number of circulating CD8+ T-cells increased and CD4+ T-cells decreased in heavy smokers. This abnormality was reversible upon discontinuation of smoking. A low CD4+/CD8+ ratio is a characteristic of the systemic inflammation seen in COPD and it is genetically controlled [88]. It is possible then, that in genetically predisposed smokers, tobacco initiates a state of generalised, chronic inflammation [89–91]. Because the toxic effects of tobacco extend to other organ systems, it is no surprise that the most common comorbid conditions associated with COPD are cardiovascular disease and cancer [19, 20, 92–94]. In a study by Soriano *et al.* [95], 2699 patients with COPD were identified. Compared with controls, the patients had a higher comorbidity burden, particularly cardiovascular diseases, osteoporosis and cataracts. The association of comorbidities (measured with the Charlson index [97]) with mortality was described by Almagro *et al.* [96] in a study of hospitalised COPD patients. A higher Charlson index was an independent predictor of mortality ($p<0.001$). In a recent study, de Torres *et al.* [98] assessed the outcome of 747 patients with COPD followed for 30 months on average. They observed that the COPD-specific comorbidity test (COTE) index added significantly to the capacity of the BODE index to predict mortality. Whether the COTE index or any other should be added to COPD to grade disease severity remains to be studied.

Multidimensional mortality risk assessment in COPD

For many years now, FEV1 and age have been considered to be the most important prognostic indicators in COPD. Unfortunately, both are progressive and, for the most part, irreversible. Most studies evaluating the effectiveness of therapies in COPD have focussed on this physiological outcome and the failure of most therapies to increase or delay the rate of decline of FEV1 has led to nihilism. However, the evidence presented in this chapter suggests that multiple factors other than FEV1 are also associated with mortality in COPD. These factors are reflections of the local and systemic involvement of COPD, and many of them are amenable to treatment [99–111]. Sole reliance on FEV1 to evaluate COPD progression leads to an incomplete assessment and makes any attempt to change COPD progression difficult to achieve.

It is reasonable then, that a composite index that incorporates important predictors of mortality, reflecting not only impairment in lung function but also systemic consequences of the disease, may provide a more comprehensive way to evaluate COPD [112]. The use of multidimensional indices for the prediction of disease severity and mortality has been used in other areas. Perhaps the best known are the tumour size (T), node involvement (N) and presence of metastasis (M) or TNM staging for lung cancer [113, 114], or the APACHE

(Acute Physiology and Chronic Health Evaluation) score used in the grading of disease severity and prognosis in patients admitted to intensive care units [115].

In a previous study, we assessed 207 patients with COPD, measuring variables that predict mortality [34]. These included: age, sex, smoking history in packs per year, FVC, FEV_1, dyspnoea measured using the mMRC dyspnoea scale, BMI, functional residual capacity, IC, and haematocrit and albumin level. After 1 year, we had identified four variables that more strongly predicted risk for death: BMI (B), airflow obstruction (O) as measured using FEV_1, dyspnoea (D) as measured using the MRC dyspnoea scale, and exercise capacity (E) as measured using the 6MWT. These variables, which have a strong statistical association, biological plausibility and ease of administration, were incorporated into a multidimensional scale that ranged from 0 (least risk) to 10 (highest risk) (table 1) [34]. The BODE index was prospectively validated in a separate cohort of 625 patients with COPD who were evaluated every 6 months for ⩾2 years, or until death. We found that each unit of BODE increase raised the risk of death by 33%. When integrated into numerical quartiles, those patients with a BODE index in quartile 4 (BODE index score of 7–10) had a mortality rate of 80% at 52 months. In addition, using receiver operating characteristic (ROC) curves, the study indicated that the BODE index was a better predictor of mortality than any of the individual variables alone. Not only was all-cause mortality predicted but more importantly, the association of the BODE index was even stronger with death from respiratory causes, supporting the premise needed to develop a COPD staging system.

The predictive value of the BODE index has been tested by other investigators using different outcomes [116–133]. All of these studies have found BODE to be a good predictor of all-cause and respiratory mortality and some of exacerbations and hospitalisations.

In order to summarise the voluminous information related to BODE, we will address the value of BODE to predict outcome, review the other multidimensional indices that have been developed, and then consider the BODE index as a tool to monitor response to disease progression or response to therapy.

BODE and other indices as a COPD prognostic and staging tool

Following its initial publication, many reports have tested the prognostic value of BODE. Ong *et al.* [130] recruited 127 COPD patients with COPD and determined their BODE

Table 1. Calculation of the BODE index

Variable	**Points on BODE index**			
	0	**1**	**2**	**3**
FEV_1 % pred	⩾65	50–64	36–49	⩽35
6MWD m	⩾350	250–349	150–249	⩽149
mMRC dyspnoea scale	0–1	2	3	4
BMI	>21	⩽21		

Points from each variable are added according to the threshold value measured for each one. The value ranges from 0 to a maximum of 10. % pred: % predicted; mMRC: modified Medical Research Council. Reproduced and modified from [34].

index. After 2 years, the investigators found the median BODE score to be lower among survivors than nonsurvivors (4 *versus* 6; $p=0.003$) and noted a significant effect of the BODE score on mortality (hazard ratio (HR) 1.30 (95% CI 1.08–1.56); $p=0.006$). BODE also predicted hospitalisation. After this initial report, several groups explored the predictive value of other multidimensional indices, as shown in table 2.

Puhan and colleagues developed the ADO index [132], which included age, dyspnoea and degree of airflow obstruction. In addition, they updated the BODE index, increasing the predictive value of the 6MWD value by giving it a higher weight in the index. The ADO and modified BODE index were both predictive of all-cause mortality, better than the original BODE index. However, no other outcome except all-cause mortality was evaluated.

Soler-Cataluna *et al.* [133] developed the BODEx index in which 6MWD was substituted for exacerbations. This index was a good predictor of mortality in 185 patients and performed as well as the original BODE index. However, the sample was small and only all-cause mortality was evaluated.

Three other variations on the BODE index have been developed: the m-BODE, in which exercise was measured using V'_{O_2} instead of 6MWD [134]; the i-BODE, in which the incremental shuttle walk test was used instead of 6MWD [135]; and the BODEm, in which the San Diego dyspnoea score was used instead of the mMRC dyspnoea scale [80]. All of these indices performed as well as the original BODE index with all-cause mortality as the outcome. Again, no other outcome was evaluated and there was no validation cohort.

Another index that incorporated exacerbations was developed: the DOSE index included dyspnoea, obstruction, smoking and exacerbations [136]. This eight-point scale predicted health status and exacerbations but was not tested for mortality.

The DOREMI BOX, or dyspnoea, rate of exacerbations, exercise, BMI and oxygenation, had a good predictive capacity for death in a small cohort over a long period of follow-up [137].

The HADO index integrated a health status questionnaire, activity (also determined by a questionnaire), dyspnoea and degree of obstruction [138, 139]. Once again, the only outcome was all-cause mortality. However, comparison with the original BODE indicated that the BODE was better in patients with a lower FEV_1 (<50% pred), while HADO predicted well in milder patients.

The CPI score, which includes quality of life, obstruction, age, BMI, exacerbations and cardiovascular disease, is complex. It was derived from a very large database and predicted death, hospitalisation and exacerbations, but no test for respiratory mortality was reported [140].

Other indices have had more methodological problems and poor validation; these include the COPD severity score or COPDSS, which was based on self-reported diagnosis of COPD in 265 patients [141]. The score predicted future hospitalisations. The PILE index, comprising leg strength, IL-6, airflow obstruction and speed over 400 m was a good predictor of all-cause mortality in a population of 271 patients aged 70–79 years followed for 5 years [142]. The SAFE index, which includes the St George's questionnaire, airflow limitation and exercise performance, was evaluated in only 86 patients with exacerbations as the outcome [143], and the TARDI index [144], which has age, BMI, dyspnoea, cardiovascular risk, hospitalisations

Table 2. Components of the different multidimensional indices of COPD

	Pulmonary					Extrapulmonary					
	Respiratory symptoms			Lung function							
	Dyspnoea	Exacerbations	Health status	FEV1	Oxygen	Age	Smoking	BMI	Exercise	Comorbidities	Biomarkers (serum)
ADO	X			X		X					
BODE	X			X				X	6MWD		
BODEx	X	X		X				X			
BODEm	X[#]			X				X	6MWD		
i-BODE	X			X				X	Shuttle test		
m-BODE	X			X				X	V'_{O_2}		
CPI		X	X	X		X		X		Cardiovascular	
CODEX	X	X		X						Charlson	
DOREMI BOX	X	X		X	X			X	Movement intolerance		
DOSE	X	X		X			X				
HADO	X		X	X					Physical activities Questionnaire		
PILE				X					Speed >400 m		IL-6
SAFE			X	X					6MWD		
TARDI		X[¶]		X		X		X		Cardiovascular	

V'_{O_2}: oxygen uptake. [#]: San Diego dyspnoea; [¶]: hospitalisations.

and FEV_1 amongst its components, evaluated over 3341 patients in Scotland. The index did predict all-cause mortality over 3 years but no organ-specific outcome was evaluated.

A summary of these indices, their methodology and predictive value is shown in table 3.

More recently, the importance of comorbidities in the outcome of patients with COPD has been recognised [1, 19, 92–94, 147]. This has led to efforts to incorporate them into the prognosis of COPD (table 4). The CODEX index incorporated comorbidities (measured using the Charlson index), degree of airflow obstruction, dyspnoea and previous severe exacerbations; it predicted all-cause mortality better than the BODEx or the ADO index after hospital discharge in a cohort of patients with COPD [148]. DE TORRES *et al.* [98] studied the COPD-specific comorbidity index or COTE index plus the BODE index in a cohort of 707 patients followed over 50 months. The C statistic in this study still offers the highest value reported at 0.81 (95% CI, 0.77, 0.86) compared with the ABCD (AUC of 0.61) grading system proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the BODE index alone (AUC of 0.71).

A few studies have attempted to compare several of these indices across a larger spectrum of patients. The COPD collaborative cohorts to assess multicomponent indices (COCOMIC) group in Spain collected data from several cohorts consisting of >3000 patients in total, followed for up to 10 years [125]. In this analysis, the ADO had the best predictive power for all-cause mortality, but when the indices that did not include age were adjusted for age (an excellent predictor of death by itself), the BODE and its modifications (m-BODE, BODEx) had similar properties. Other authors have reviewed the literature and offered certain conclusions. VAN DIJK *et al.* [149] found a total of 13 indices in the literature. The authors attempted to grade them in various aspects and concluded that few had been well validated (sufficient number of patients, a derivative and a validating cohort, solid outcomes, sufficient follow-up). All of the studies had something in common, none had been tested to see whether their implementation improved outcome. The authors recommended that the creation of more indices should stop; instead, efforts should be put into planning and completing studies designed to test whether incorporating any index improves care of patients with COPD. This statement has been supported by others [150–152].

BODE: a tool to evaluate COPD progression or response to therapy

The first evaluation of BODE as a tool to evaluate COPD progression was completed by IMFELD *et al.* [122] who showed that post-operative BODE predicted 5 year survival in 186 patients following LVRS (HR 0.497 (95% CI 0.375–0.659); $p<0.001$). Using ROC analysis, the BODE index predicted survival better (0.74) than the FEV_1 (0.63). This concept was better tested by MARTINEZ *et al.* [127] in the NETT. The study randomised >1000 patients with inhomogenous emphysema to either LVRS or medical treatment, including PR. LVRS resulted in significant BODE improvement compared with the medical arm. More importantly, a decrease of 1 unit of BODE at 6 months predicted survival at 1, 2 and 5 years after randomisation, whereas an increase in 1 unit was associated with decreased survival. These results suggest that the BODE index can be used not only as a surrogate of mortality but as a tool for disease modification. To this effect, other interventions have also modified BODE. Based on the observation that rehabilitation improves variables included in BODE, it was hypothesised that PR would be able to modify the severity of COPD and the risk for

Table 3. Comparison of different multimorbidity indices in patients with COPD

Index [ref.]	Derivative cohort	Validating cohort	All-cause mortality	Respiratory mortality	Exacerbations	Disease progression or response to intervention
BODE [34, 98, 119–122, 126–131, 135, 139, 145, 146]	Yes	Yes	Yes	Yes	Yes	Yes
BODEx [133]	Yes	No	Yes	No	Yes	No
m-BODE [134]	Yes	Yes	No	No	No	No
i-BODE [135]	No	Yes	Yes	No	No	No
ADO [132]	Yes	Yes	Yes	No	No	No
DOSE [136]	Yes	Yes	No	No	Yes	Yes
CPI [140]	Yes	Yes	Yes	No	Yes	No
HADO [138, 139]	Yes	No	Yes	Yes	No	No

BODEx: 6MWD is substituted by exacerbations; m-BODE: 6MWD is substituted by peak oxygen uptake; i-BODE: 6MWD is substituted by the incremental shuttle walk distance; ADO: age, dyspnoea, obstruction index; DOSE: dsypnoea, obstruction, smoking status, exacerbations index; CPI: COPD, prognostic index; HADO: health status, activity, dyspnoea, obstruction index.

Table 4. Comparison of multidimensional indices that include a comorbidity evaluation

Multidimesional index + comorbidities	Derivative cohort	Validating cohort	All-cause mortality	Respiratory mortality	Exacerbations	Disease progression or response to interventions
CODEX [148]	Yes	Yes	Yes	No	Yes	No
BODE+COTE [19, 98]	Yes	Yes	Yes	Yes	No	No

CODEX: Comorbidity (Charlson index), obstruction, dyspnoea and exacerbations index; COTE: COPD, comorbidity test index.

mortality, as measured by the BODE Index [75]. In this study, of the 246 patients who qualified for and were offered rehabilitation, 116 accepted and completed the 21-session rehabilitation programme; 130 declined participation. Patients were followed for >2 years or until death. After graduation from PR, the BODE index decreased significantly from 5.07 to 4.18. This resulted in a "shift" from the third quartile to the second quartile, and their initially predicted mortality of 20–30% changed to an observed mortality of 11.2%. Patients who declined PR had a worse BODE index at entry (6.9) and had the highest mortality rate (50%). For patients who responded to PR, BODE improved by a statistically significant 25% at 3 months, compared with the patients who did not respond to rehabilitation. In Australia, Bu *et al.* [145] enrolled 56 patients with COPD in an observational study, following them for 2 years. BODE worsened in a total of 33 patients; it remained unchanged in 18 and it improved in five. Patients whose BODE index increased had more frequent exacerbations and hospitalisations, and their hospital stays were longer.

Patients with advanced COPD experience exacerbations and hospitalisations that are usually associated with poor outcome [153]. Cote *et al.* [120] assessed the impact of exacerbations on patient-centered outcomes, including BODE. In this study, 205 patients were recruited and were evaluated with the BODE index at baseline while stable, during the exacerbation event and every 6 months thereafter. A total of 130 patients experienced exacerbations and 75 patients remained exacerbation free for the duration of the study. Exacerbators showed a worsening of BODE index of 1.38 points during the exacerbation event and although there was a partial improvement, the BODE index at 24 months remained 1.09 points above baseline. Nonexacerbators showed a negligible increase in BODE at 2 years (0.07 points), which differed significantly from that of the exacerbators ($p<0.001$). Finally, using >700 patients in the BODE cohort, Casanova *et al.* [146] compared the prognostic validity of longitudinally followed FEV1 and BODE. The change in BODE over time had less variability than the variability of the FEV1 and was a better predictor of mortality than any of the individual variables that integrate the BODE.

Taken together, results from these studies indicate that the BODE index not only reflects changes on disease severity but is also a marker of outcome, suggesting that the BODE index can be used as a surrogate marker for mortality, a staging tool and a tool to assess disease modification.

Conclusion

Although FEV1 remains the most important indicator of the severity of airflow obstruction in COPD, other markers of mortality in COPD are becoming more accurate. Chief among these predictors of mortality are dyspnoea, exercise capacity and BMI. Evidence also PH hypertension and hyperinflation, among others. The validated multidimensional BODE index and other indices incorporate the predictive validity of the best of these potential surrogates into a single measure of disease severity and survival. The BODE index and other multidimensional staging tools may prove to be valuable tools not only in the assessment of severity and progression of disease, but also in the evaluation of the response to therapeutic interventions. Implementation studies are needed to determine their clinical value.

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What is bacterial colonisation in COPD?

Arjun Mohan[1,2] and Sanjay Sethi[1,2]

Case history: A 62-year-old male presents with chronic exertional dyspnoea, early morning productive cough and intermittent wheezing. He is a former smoker with a smoking history of 40 pack-years. He states that his symptoms are gradually progressive, he does have "bad days of increased dyspnoea, cough and sputum" quite often, but he does not seek medical care for them as he does not want to bother his doctors. Instead, he increases his inhaled bronchodilators and reduces his activities until these episodes resolve. He has had only one medically treated exacerbation in the past year, when he had to come to the emergency room because his breathing "got really bad". Spirometry shows severe airflow obstruction without a bronchodilator response. His outpatient medication includes a tiotropium inhaler once daily and a budesonide–formoterol inhaler twice a day. Sputum cultures carried out at this visit show 3+ Nontypeable *Haemophilus influenzae* (NTHi). What is the significance of his sputum culture results? How did he get colonised with NTHi, is it of clinical significance, and does it need treatment? If yes, how do we treat such colonisation?

Chapter summary: It is likely that chronic bacterial presence in COPD airways, usually referred to as colonisation, is in fact a chronic infectious state. Several investigations have now demonstrated that the presence of bacteria in the lower respiratory tract in stable COPD is associated with increased inflammation. Pathological and radiological findings in COPD support chronic infection, as do recent mouse models. Increased daily respiratory symptoms and unreported exacerbations are clinical manifestations of chronic infection in COPD. Chronic infection in this disease results from multiple impairments of innate lung immunity induced by exposure to noxious particles or gases such as tobacco smoke.

The role of bacterial colonisation and infection in COPD has been debated since the 1950s [1]. The pendulum has swung in both directions. Before the crucial role of exposure to noxious particles and gases (*i.e.* tobacco smoke, occupational exposures and biomass exposure) was identified, bacterial exacerbations and mucus hypersecretion were thought to cause of COPD, as embodied in the "British hypothesis". In the 1970s and 1980s, the pendulum swung in the other direction and the role of bacteria was reduced to an epiphenomenon in COPD, implying bacteria were of little consequence in exacerbations and in stable disease. This paradigm shift came about for several reasons. Studies, such as those by FLETCHER and PETO [2], did not show a correlation between mucus hypersecretion

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and exacerbations with a loss of lung function. The central role of tobacco smoke in COPD became apparent. Longitudinal sputum culture based investigations demonstrated no difference in bacterial isolates from sputum during exacerbations and stable disease. Similarly, limited immunological studies showed no differences in immune responses to bacteria [3]. The "Dutch hypothesis" of COPD emerged and the attention shifted to the role of an allergic diathesis underlying COPD.

Over the past two decades, the pendulum has swung back to the middle. Initially, there was a redefinition of bacterial causation of exacerbations, with the understanding that bacterial exacerbations are related primarily to the acquisition of new strains of bacteria from the environment. This topic has been reviewed in previous publications [4]. Subsequently, evidence emerged demonstrating that the presence of bacteria in the lung in stable disease, referred to as bacterial colonisation, was not innocuous. This concept has been embodied in the "vicious circle hypothesis", and will be discussed in this chapter (figure 1). Although it is sometime thought to be a re-embodiment of the British hypothesis, it differs from it in several important aspects. The vicious circle hypothesis recognises the fact that tobacco smoke or another noxious exposure is essential for, and therefore central to, the development of COPD. Lung damage and progression of COPD induced by bacteria is thought to be related to inflammation caused by the bacteria in the "colonised" stable state, with this inflammation periodically exaggerated during exacerbations.

What is meant by bacterial colonisation?

A bacterial pathogen is deemed to be colonising a human niche, usually on the skin or mucosal surfaces, if its presence is not associated with disease, thus differentiating it from an infection. Specifically, colonisation is associated with a lack of damaging effects to the host attributable to the pathogen, as well as the absence of a specific immune response that aims to eradicate or limit the pathogen. Such colonisation is normal on the skin and mucosal

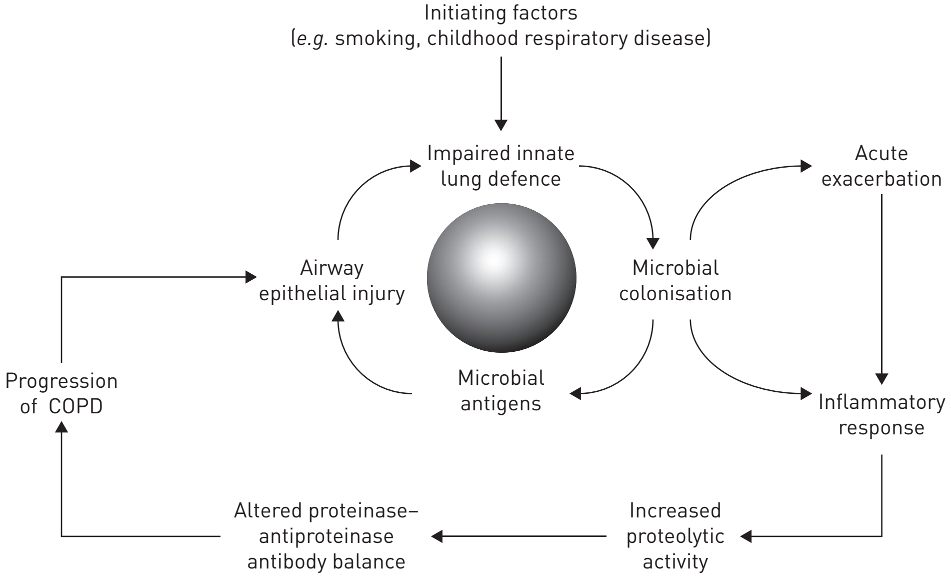
Initiating factors
(*e.g.* smoking, childhood respiratory disease)
Impaired innate lung defence
Acute exacerbation
Airway epithelial injury
Microbial colonisation
Progression of COPD
Microbial antigens
Inflammatory response
Altered proteinase–antiproteinase antibody balance
Increased proteolytic activity

Figure 1. The "vicious circle" hypothesis. Reproduced from [4] with permission from the publisher.

surfaces, and involves specific well known bacterial species such as *Staphylococcus epidermidis* on the skin and *Escherichia coli* in the gut. The presence of bacteria in the lung in stable COPD, although clearly abnormal, got labelled as "colonisation" not because of a demonstration of its innocuous nature, but rather to differentiate it from an "exacerbation". In an exacerbation, the lung bacteria were thought to be causing an infection. Therefore, in the stable state, they were "colonisers". The absence of the increased respiratory symptoms that characterise an exacerbation became the defining criteria for "colonisation" in COPD. As discussed later in this chapter, the presence of bacteria in stable COPD is not innocuous, and therefore, has been mislabelled for quite some time.

Difficulties in assessing bacterial colonisation in the lung

In order to critically examine the published literature on bacterial colonisation in COPD, it is imperative to assess several methodological details that can profoundly impact the results. First, which lung compartment was sampled? Was it expectorated or induced sputum, the luminal contents of the large airway, those of the small airway, the alveolar space or the lung parenchyma. It has been shown that the microbial flora in each of the lung compartments differs in the same individual [5]. Sputum samples are easy to collect, can be sampled repeatedly in a longitudinal fashion and have real world applicability. However, they are easily contaminated with upper respiratory tract flora and primarily reflect the large airway milieu. Bronchoalveolar lavage (BAL), obtained by bronchoscopy, and protected brush samples provide deeper lung samples of medium-to-small airways and/or the alveolar space. If properly collected with careful attention to avoid upper airway contamination, they can reflect the true microbial milieu of the lower respiratory tract in COPD. Limitations include the inability to sample repeatedly, the risk and therefore the inability to sample patients with severe obstructive disease (unless they are intubated), and the microbial heterogeneity that has been described in different parts of the lung [6]. Finally, surgically obtained and resected, explanted lung samples have been studied to look at microbial flora in the lung parenchyma. These specimens tend be difficult to collect and have sparse microbial flora.

A second important issue is how were the bacteria identified in the sample? Sensitivity and specificity differ substantially between traditional cultures and non-culture based detection techniques that rely on the detection of bacterial DNA, such as PCR and 16s rRNA microbiome assessment. Culture independent molecular techniques are becoming a popular tool to identify bacteria in COPD studies. These new diagnostic techniques have consistently shown enhanced sensitivity for bacteria when compared with traditional bacterial culture methods [7–9]. However, this exquisite sensitivity results in susceptibility to contamination and difficulties in interpretation of very low concentrations of bacteria. Furthermore, 16s microbiome assessment can, at best, differentiate to the species level and important strain differences are therefore missed with this technique [10]. Finally, traditional culture techniques provide a bacterial isolate that can then be used to study host immune responses or virulence characteristics. Such studies can support the role of these bacteria as infectious pathogens and can also contribute to vaccine development. Non-culture techniques do not provide an isolate to study and therefore the precise role of the pathogens identified by these techniques is difficult to discern.

Patterns of bacterial colonisation in COPD

Most studies of bacterial colonisation in COPD have used bronchoscopic sampling with brushings or BAL. When such samples were examined by conventional culture techniques with a focus on potential pathogenic bacteria, there was clearly increased bacterial colonisation in the lung in stable COPD [11, 12]. Some recent studies using microbiome techniques on this type of sample have shown that the composition of the microbiome differs from controls, but that the concentrations of bacteria may not be greater in COPD. However, scrupulous attention to avoid upper airway contamination was not consistently implemented in these studies, making them difficult to interpret. In addition, the focus of these studies was the entire microbiota in the sample, not just potential pathogens.

In conventional microbiology studies of bronchoscopic specimens, potential pathogenic bacteria have been detected in about a third of stable COPD patients at concentrations of ⩾100 $\text{CFU}\cdot\text{mL}^{-1}$, while this is seen in <10% of nonsmoking healthy controls [11, 12]. The most common potential pathogenic bacteria isolated in COPD are the same as those seen during exacerbations, nontypeable *Haemophilus influenzae* (NTHi), *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*. Interestingly, this colonisation with potential pathogenic bacteria appears to happen early in COPD, as colonisation with potential pathogenic bacteria was observed at a similar frequency among the healthy smokers used as controls in another study [13]. When these four major pathogens were detected in stable COPD sputum specimens using real time PCR, 29% of samples contained one or more of these potential pathogenic bacteria. Conventional cultures of the same specimens yielded these bacteria in only 8% of the sputum samples [14]. In studies of lung specimens with microbiome techniques, changes observed in stable COPD include a loss in diversity, which worsens with increasing severity of COPD [15]. Such loss of diversity has also been demonstrated in the upper respiratory tract of smokers when compared with nonsmokers [16]. Changes in the distribution of bacterial phyla in COPD have also been described in these studies, including increases in *Firmicutes* and *Proteobacteria*.

Consequences of bacterial colonisation in COPD

Host inflammatory response

As the lower respiratory tract is not adapted to the chronic presence of bacteria in significant quantities, there should be a vigorous host immune-inflammatory response in an attempt to minimise or eradicate these bacteria in COPD. Therefore, if bacterial presence in the lower airway in COPD was not a true colonisation, the level of the local host inflammatory response should be higher with bacterial colonisation. Multiple studies by various investigators have shown that the host inflammatory response, as reflected by concentrations of inflammatory cells and cytokines, is indeed much higher in colonised COPD patients than in non-colonised COPD patients with similar degree of airflow obstruction [17–19]. Furthermore, exaggerated host inflammation with bacterial colonisation appears to span the course of the disease. It has been seen in smokers without COPD and persists even after COPD patients quit smoking [13, 20]. Several mediators and cells have been reported to increase with bacterial colonisation, including neutrophils, CXCL8 (IL-8), leukotriene B4, myeloperoxidase, matrix metalloproteinase 9, TNF-α, IL-6 and neutrophil elastase [13, 17, 20–23]. This neutrophilic pattern of inflammation has been strongly associated with COPD progression, with chemokine-induced neutrophilic infiltration releasing proteolytic mediators that can damage host tissues [24–26].

Bacterial molecules can upregulate several transcriptional regulators that mediate inflammation in COPD [27, 28]. Of these, the most prominent is nuclear factor-κβ; however, others such as transforming growth factor-β, Smad, p38 mitogen-activated protein kinase and phosphoinositide 3-kinase could also be significant [29]. Mucus hypersecretion and accumulation have been linked to COPD progression and worse outcomes, and bacterial components, such as the P6 outer membrane protein of NTHi, can upregulate the mucin production pathway in airway epithelium.

Pathological and radiological consequences

Recent investigations into the pathology of the airways across the range of COPD severity, as well as studies in mouse models of COPD, strongly support the notion of a specific host immune inflammatory response to chronic colonisation in this disease. Hogg *et al.* [30] demonstrated that the strongest correlate of worsening airflow obstruction was the development of lymphoid aggregates in the small airways, predominantly composed of B-cells. These lymphoid aggregates could represent either a local host immune response to chronic microbial infection or a local autoimmune response to smoke-induced autoantigens. A local host immune response to a chronic microbial infection is supported by observations in mouse models of COPD. Moghaddam *et al.* [31] noted development of very similar looking lymphoid aggregates following repeated lung instillation of bacterial (NTHi) lysate, but not with chronic cigarette smoke exposure. However, in this model, emphysema and mucus metaplasia are not seen. When both insults are combined in a mouse model, *i.e.* smoke exposure and repeated instillation of NTHi lysate, then the entire spectrum of COPD-associated pathological changes seen in humans is replicated, including emphysema, mucus metaplasia and lymphoid aggregates [3].

Radiological phenotyping of COPD has also yielded observations that support a damaging effect of chronic colonisation in COPD. Bronchiectasis is classically regarded as a disease induced by chronic infection of the bronchi and, today, is readily diagnosed using HRCT. When HRCT has been systematically applied to COPD patients, an appreciable prevalence of bronchiectasis is seen in all studies, and in some studies, more than half of stable moderate or severe COPD patients have bronchiectasis [32]. The notion that this bronchiectasis is related to chronic bacterial colonisation is supported by a significant association between the presence of bronchiectasis in these patients and chronic colonisation with potential bacterial pathogens on repeated sputum sampling (predominantly NTHi and *P. aeruginosa*) [32]. COPD patients with bronchiectasis were more likely to have chronic bronchitis and be hospitalised, and had worse airflow obstruction and an increased mortality [33].

Clinical consequences of bacterial colonisation in COPD

By definition, bacterial colonisation in COPD is not associated with a clinical exacerbation that is reported and requires treatment. In studies of bacterial exacerbations, a fairly good correlation between the magnitude of increased respiratory symptoms and of increased airway inflammation was noted [20]. Bacterial colonisation causes increased airway inflammation, therefore, we hypothesised that an accurate quantification of daily COPD symptoms would show them to be increased by bacterial colonisation.

In a longitudinal cohort of COPD patients, symptoms were measured on a daily basis using the breathlessness, cough and sputum scale, while colonisation was assessed by sputum culture and real-time PCR every 2 weeks [14]. A significant association was found between the level of daily respiratory symptoms and bacterial colonisation (figure 2). This association

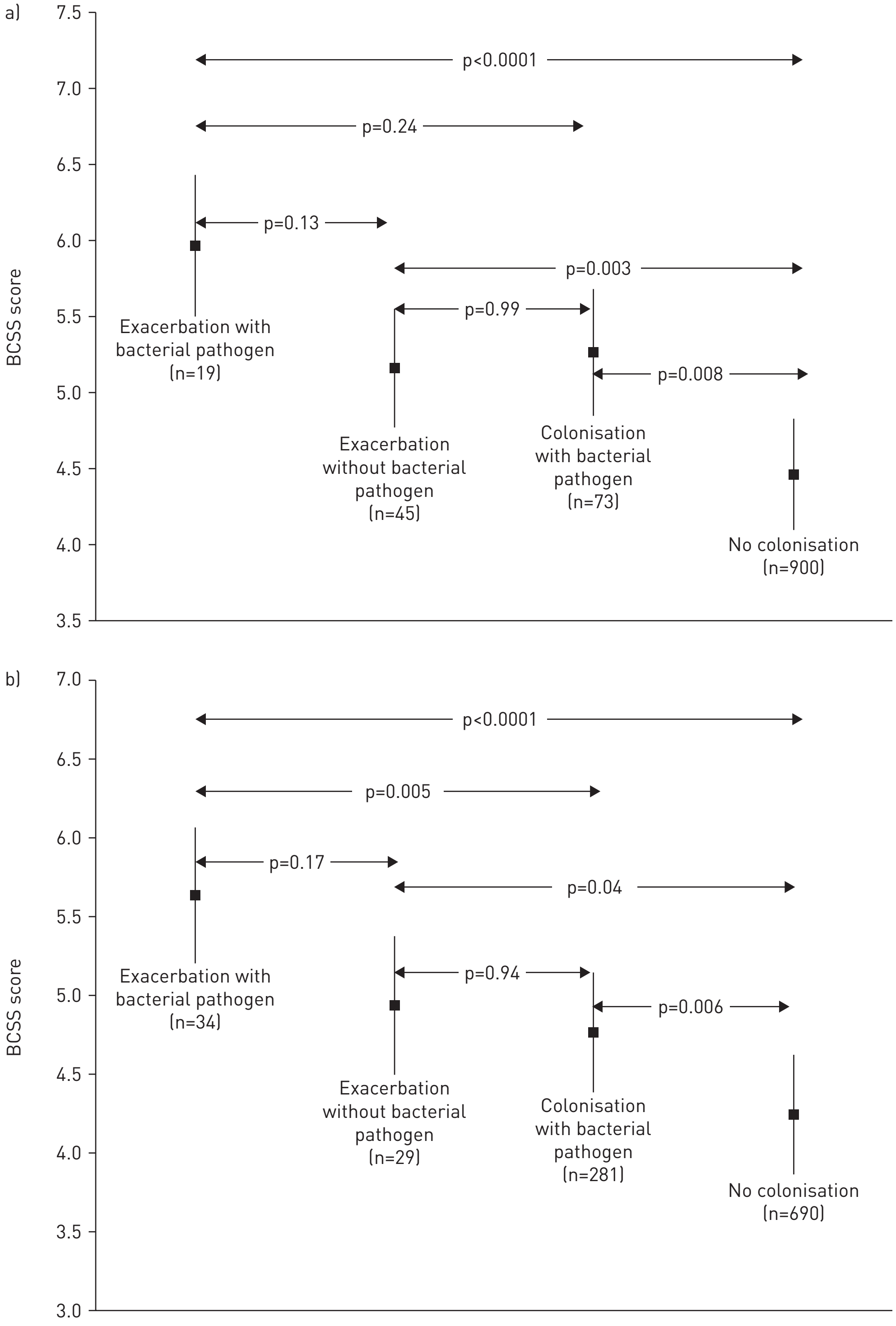

Figure 2. Breathlessness, cough and sputum scale (BCSS) score during exacerbation and colonisation as assessed using a) sputum cultures and b) PCR to detect bacterial pathogens. BCSS scores are presented as mean±SE. Reproduced from [14] with permission from the publisher.

was not merely a statistical one, as the magnitude of increase in symptoms with colonisation was similar to that seen in mild exacerbations. When we measured airway inflammation in these samples, sputum IL-8 levels also increased during episodes of bacterial colonisation. It is quite likely that a proportion of the exacerbations that COPD patients fail to report are related to episodes of bacterial colonisation and mild viral infections. Unreported exacerbations have been associated with worse health status in COPD.

Vicious circle hypothesis

As discussed earlier, evidence continues to accumulate that a "vicious circle" of bacterial airway colonisation and inflammation exists in COPD (figure 1) [3, 4, 34]. In this aspect, COPD therefore resembles bronchiectasis and CF, airway diseases in which chronic infection is thought to be the primary driver of disease progression. However, important differences between the role of infection in COPD and these disorders should be noted. COPD is very heterogeneous disease, and it is likely that the vicious circle is significant only in certain subgroups of COPD patients, such as those with chronic bronchitis, bronchiectasis on CT, repeated infectious exacerbations, *etc*. Another important difference in the vicious circle of COPD is that infection it is not the primary inciting event. Rather, the primary event initiating COPD is inhalation of noxious particles or gases, which cause multiple impairments of the innate lung defence, allowing establishment of chronic infection. The inflammatory immune response that attempts to clear this infection is ineffective, but does further disrupt innate lung defence, establishing the vicious circle.

Mechanism of bacterial colonisation in COPD

The contrast between the upper airway above the glottis and the tracheobronchial tree in terms of resident bacterial flora is quite dramatic. Bacteria are normally resident in large numbers in the upper airway and these are microaspirated into the tracheobronchial tree as a normal occurrence. In addition, bacteria and other microbes are constantly introduced in to the lung with breathing. In spite of exposure to this considerable microbial load, healthy lungs are sterile by conventional culture techniques. The much more sensitive microbiome techniques, when applied to carefully obtained samples, reveal a sparse microbiota in the healthy lung. Most probably, this microbiota represents transient colonisation while the microbes from microaspiration or inhalation are being eliminated.

This ability of the lung to maintain relative sterility is attributed to its intricate, redundant and highly effective innate lung defence system. Exposure to tobacco smoke and consequent inflammation causes multiple defects in the innate lung defences, these defences are finally overcome and chronic colonisation is established. Three aspects of innate lung defence in COPD have been studied: mechanical barriers, airway antimicrobial polypeptides and airway immune cells (table 1).

Mechanical barriers

Impairment of the mechanical barriers of the lung is inevitable with cigarette smoking. Smoking reduces ciliary beat frequency, induces squamous metaplasia, and increases goblet cells and submucosal glands. Smoking also increases epithelial permeability by directly damaging epithelial junctions [35]. Once initiated, this defect appears to be self-sustaining and impairment of mucociliary clearance along with mucus hypersecretion makes an ideal

Table 1. Host immunity alterations in COPD

Mechanical barrier	Mucociliary clearance Goblet cell hyperplasia Squamous metaplasia Secretory IgA Epithelial junction	Mostly in large airways
Antimicrobial peptides	Defensins Elafins Cathelicidins Lysozymes Surfactant proteins Lactoferrin	Large and small airways
Airway cells	Alveolar macrophages Neutrophils Lymphocytes	Large and small airways

environment for bacterial colonisation. Bacterial products, including endotoxin and outer membrane proteins, not only inhibit ciliary function directly but also propagate damage to the epithelium by producing proteolytic enzymes [36–38].

Airway antimicrobial peptides

Airway antimicrobial polypeptides are soluble molecules that are naturally present in airway surface fluid and include surfactant proteins (SP), defensins, elafin, cathelicidin, lysozyme, secretory leukocyte protease inhibitor (SLPI), *etc*. They serve as an integral part of the innate immunity against bacteria and viruses, and several also possess immunoregulatory properties in addition to antimicrobial activities. SP-A and SP-D have been shown to be reduced in smokers, and even more so in patients with emphysema [39]. Deficiencies in salivary lysozyme and SLPI have been associated with higher rates of COPD exacerbation [40, 41]. However, conflicting data on increased and decreased defensins [42–44] and increased elafin [42] make it unclear if airway antimicrobial polypeptide levels reflect a cause or a consequence of bacterial colonisation.

Immune cell function

Although several cells contribute to innate lung defence, the most extensively investigated are alveolar macrophages. Alveolar macrophages play a key role in innate lung defence, and participate actively in phagocytosis and initiation of the host immune response. Both alveolar macrophage phagocytosis and inflammatory mediator secretion in response to bacterial molecules and pathogens are reduced in COPD [45]. The clinical relevance of impaired alveolar macrophage function was recently demonstrated. Impairment of cytokine secretion in response to COPD-related bacteria was greater in exacerbation prone patients than in non-exacerbation prone patients (figure 3) [46]. Progressive impairment of phagocytosis of NTHi and *M. catarrhalis* by alveolar macrophages is seen with worsening lung function in COPD, which coincides with a progressive increase in exacerbation frequency [46].

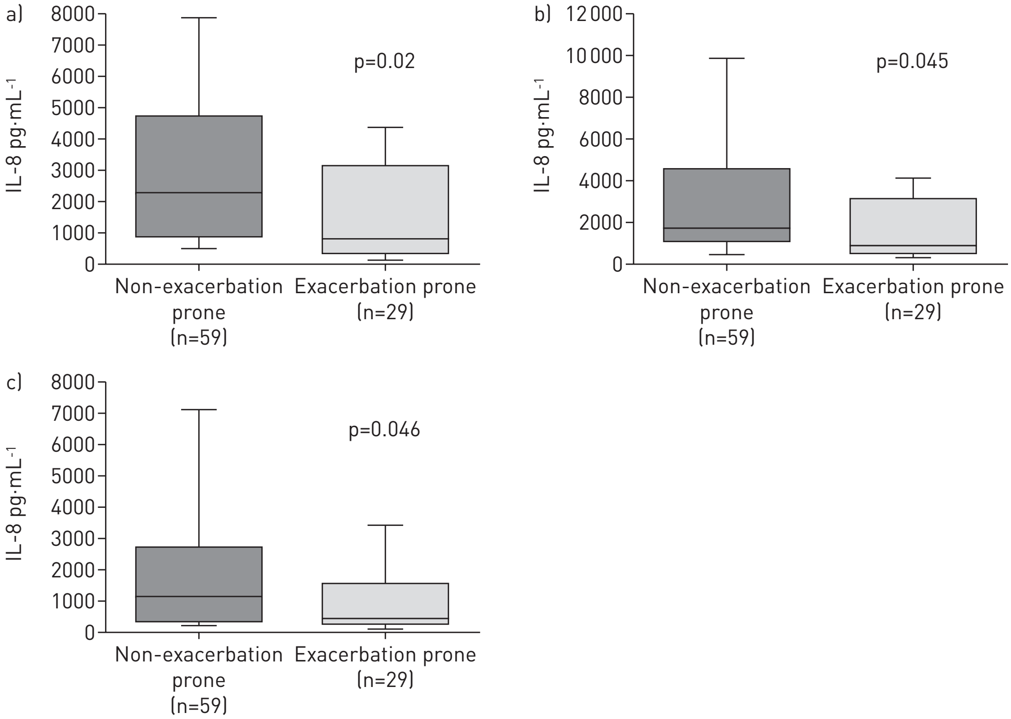

Figure 3. Alveolar macrophage IL-8 response to a) *Haemophilus influenzae*, b) *Moraxella catarrhalis* and c) *Streptococcus pneumoniae* in exacerbation prone and non-exacerbation prone COPD patients. Boxes represent the interquartile range, with the horizontal line in each box representing the median value. Vertical bars represent the 10–90th centile range. Reproduced from [46] with permission from the publisher.

Alveolar macrophages have several surface receptors that coordinate the cell's response to a specific microbe and activate a number of intracellular pathways, including pattern recognition receptors (*e.g.* toll-like receptors (TLRs)) and scavenger receptors (*e.g.* MARCO) [47, 48]. Decreased expression of TLR-2 and TLR-4 has been noted in smokers as well as in patients with COPD [49, 50]. Exacerbation prone patients had significantly reduced TLR-2 upregulation in response to bacterial stimulation when compared with non-exacerbation prone patients [46]. Expression of MARCO, a scavenger receptor that mediates macrophage binding to and phagocytosis of bacteria, is impaired with cigarette smoking and in COPD [51, 52].

Conclusion

The accumulated data supports changing the paradigm that chronic microbial presence in COPD is "infection" rather than "colonisation". However, there are still large gaps in our knowledge. Bacteria vary greatly in virulence and pathogenicity. Therefore, not all bacteria will be pathogens in COPD and the rest may be true commensals. Identification of which species are pathogens in COPD and which are true commensals still needs to be determined. Although bacterial colonisation clearly is inflammatory in COPD, the causal relationship between bacterial colonisation and COPD progression is still unproven. Most of the evidence is cross-sectional and associative. Mechanistic studies in appropriate animal models, longitudinal natural history studies in COPD or studies with interventions that decrease bacterial colonisation and measure disease progression are necessary to firmly prove or dispute the vicious circle hypothesis.

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Chapter 12

Non-tuberculous mycobacterial lung disease and COPD

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Case history: A 53-year-old woman with COPD has had a cough with sputum for the last 8 years and received maintenance ICS therapy. She suffered from recurrent episodes of exacerbation of airway symptoms, often requiring antibiotic therapy. Erythromycin has been given in the last 6 months. She presented with more severe cough, copious sputum and exertional dyspnoea. Chest CT revealed bronchial wall thickening and multifocal tree-in-bud lesions. All three sputum samples collected within 1 week grew *Mycobacterium avium* complex. Is this AECOPD, non-tuberculous mycobacterial lung disease, or both?

Chapter summary: Non-tuberculous mycobacteria (NTM) are common organisms that can infect patients with chronic debilitating lung diseases. The incidence of NTM lung disease (NTM-LD) is increasing in patients with COPD. Lung structural changes due to NTM-LD may make the host more vulnerable to NTM infection. The diagnosis of NTM-LD requires the fulfilment of both clinical and microbiological criteria. However, a correct diagnosis of NTM-LD in COPD patients is usually difficult. The decision for NTM treatment should be based on the potential risk and benefit of therapy. Particular therapeutic concerns exist, especially regarding corticosteroids and macrolides. Since the presence of NTM may lead to worsening lung function and AECOPD, the outcome of patients with concomitant NTM-LD and COPD is likely to be worse. However, significant controversy exists in many areas, and further longitudinal studies are urgently needed.

Non-tuberculous mycobacteria (NTM), also known as atypical, opportunistic or environmental mycobacteria, are commonly occurring organisms that may be recovered from various environmental reservoirs like soil, tap water and dust [1]. Once considered contaminants of respiratory specimens, NTM can cause chronic debilitating lung diseases in humans, especially in susceptible hosts, including patients with structural lung diseases, such as COPD [2]. The incidences of COPD and NTM lung disease (NTM-LD) are both increasing, and the two may sometimes act in collusion. The diagnosis of NTM-LD is complicated [2] and is even more difficult in COPD patients due to overlapping symptoms and signs. Establishing the diagnosis of NTM-LD does not require

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anti-NTM therapy [2]. A clear understanding of these two diseases and their interactions is critically important for the best care of patients with concomitant NTM-LD and COPD.

The epidemiology of NTM-LD

Unlike tuberculosis (TB), public health notification is not mandatory for NTM-LD, and the significance of NTM isolates from respiratory specimens should be assessed in conjunction with the clinical context and radiological features [2]. Thus, there are few population-based data on the epidemiology of NTM-LD and much of our understanding of NTM-LD comes from evidence that is of a weak quality. Nevertheless, the available information supports the contention that NTM-LD is increasingly prevalent and its incidence is rising [3–7]. The phenomena are believed to be multifactorial. First, advances in laboratory techniques have improved the isolation and identification of NTM from clinical samples [2]. Secondly, greater awareness and better understanding of NTM-LD may prompt a more thorough investigation and follow-up of patients [8]. Thirdly, an increasing number of subjects are at risk of NTM disease, including the elderly, patients with HIV infection, those receiving immunosuppressive therapy and those with chronic lung disease [2, 9, 10]. The prolonged survival of these at-risk subjects may play a role. Fourthly, well-established diagnostic standards of NTM-LD and the availability and widespread use of chest CT are also important contributors. Fifthly, there may be a true increased exposure of humans to NTM, as evidence showing the prevalence of *Mycobacterium avium* complex (MAC) sensitisation increased from 11.2% to 16.6% between 1971–1972 and 1999–2000 [11]. Lastly, long-term and widespread use of macrolides in inflammatory airway diseases could induce bacterial succession in the respiratory tract and may also be relevant to NTM [12]. In addition, long-term macrolide use might block the ability of macrophages to lyse NTM within phagosomes and augment NTM infection [13]. Both effects could be the driver of the increased prevalence of NTM-LD worldwide.

Although first observed soon after the discovery of *Mycobacterium tuberculosis*, NTM were not widely recognised as human pathogens until the 1950s [14, 15]. The first national survey was conducted in the USA from 1979 to 1980, and indicated that NTM comprised about one-third of 32 705 mycobacterial isolates [16]. Of these, MAC (61%) was the most commonly isolated species, followed by rapidly growing mycobacteria (RGM) (19%) and *Mycobacterium kansasii* (10%). A second surveillance study performed in the USA between 1981 and 1983, showed a distribution of isolated NTM species similar to the first survey [17]. In that study, NTM disease was specifically defined and represented 38% of all reported NTM cases. Moreover, MAC (62%) and *M. kansasii* (24%) were the species most frequently associated with disease, and NTM-LD accounted for >80% of NTM disease cases. From these two surveys, the prevalence of NTM disease in the USA was estimated to be 1.8 cases per 100 000 population [18]. In the early 1990s, a study by the Centers for Disease Control (CDC) demonstrated a dramatic change in the prevalence of NTM, showing that NTM represented approximately three-fourths of mycobacterial isolates [19]. By 2005, the annual prevalence of NTM-LD in the USA was 5.5 cases per 100 000 population, with MAC accounting for >80% of cases, followed by RGM [3, 20].

Data from other nations also indicated an increase in the number of NTM isolated from clinical samples [21], even though the most commonly isolated species were changing throughout the study period of 1976–1996. In south-west Ireland, the incidence of NTM disease was 0.4 cases per 100 000 population from 1987 to 2000, and 0.62 cases per 100 000 population from 1995 to 2000 [22]. In Ireland, 53% of NTM disease cases were pulmonary and 72% of NTM disease cases were caused by MAC. In Queensland, Australia, where NTM disease is a notifiable condition, the incidence of NTM-LD also rose from 2.2 cases per 100 000 population in 1999 to 3.2 cases per 100 000 population in 2005 [6].

In a national survey in Japan, the incidence of NTM-LD was almost constant and was estimated to be 1.73 cases per 100 000 population from 1971 to 1984 [23]. In more detail, NTM-LD caused by MAC has remained stable, whereas cases caused by *M. kansasii* have increased considerably. A large mycobacterial database in Taiwan demonstrated an increasing trend of NTM-LD incidence from 3.4 cases per 100 000 population in 2000 to 13 cases per 100 000 population in 2012 [24].

Recently, the NTM-Network European Trials group reported a global study demonstrating that in pulmonary specimens, the NTM species distribution differed by continent, and by country within these continents [25]. A nationwide population-based study identified spatial clusters of NTM-LD in the USA and further detected that environmental factors related to soil and water exposure appear to increase the risk of NTM-LD [26]. Both studies, together with those listed in table 1, display the geographical and temporal diversity of NTM species causing NTM-LD. The exact reasons behind this are not fully understood but may involve differences in socioeconomic, environmental, behavioural and demographic factors [25, 26, 31]. For instance, living in coastal areas, warmer regions and areas with a higher population density have been associated with an increased risk of NTM infection [26, 32]. Working environment, particularly mining, has been described as a risk factor for NTM disease [33, 34]. In addition, host factors and varied virulence among NTM species undoubtedly have an influence.

In summary, epidemiological studies show that NTM-LD is a worldwide phenomenon with increasing presence in both developed and developing countries over the past decades. There is also marked geographical variability in the NTM species responsible for the disease.

NTM-LD and COPD together

While NTM-LD commonly occurs in structural lung diseases like COPD, bronchiectasis and CF [2], several epidemiological studies suggest that COPD is the most prevalent comorbidity, presenting in 28–42% of study subjects [7, 20, 35, 36]. In Taiwan, single-institutional experiences have implied a wide-ranging COPD prevalence in NTM-LD patients of 61% in southern areas and 16% in northern areas [37, 38]. A population-based study from Denmark found an almost 10-fold higher prevalence of COPD in NTM-LD patients (42.2%) than in population controls (4.8%) [36]. In addition, compared with NTM-colonised patients (22%) and those with possible NTM disease (29%), patients with definite NTM-LD are more likely to have COPD (37%) [7].

Recently, a single-centre study showed that 47 (19%) of 251 COPD patients fulfilled the microbiological criteria for NTM-LD [39], with RGM (49%) as the most frequently isolated species, followed by MAC (36%) and *M. kansasii* (9%). Eight (3.2%) patients had NTM-LD and received anti-NTM therapy. During exacerbations of COPD, NTM were identified in seven (1.4%) of the episodes in a study from Hong Kong [40]. Another study from the Netherlands found that sputum samples from 16 (22%) patients with COPD exacerbations yielded NTM, including four (5.4%) with two positive cultures each that grew the same

Table 1. Geographical and temporal diversity of non-tuberculous mycobacteria (NTM) species involved in NTM lung disease

Country	**Year**	**Annual incidence per 100 000 population**	**Species frequency**	**Species from respiratory samples in 2008 [25]**	
				Location	**Species frequency**
Denmark [7]	1997–2008	1.08	*M. avium* complex 57% RGM 10% *M. malmoense* 8.1%	Denmark	*M. avium* complex 54% *M. gordonae* 18% RGM 10%
France [27]	2001–2003	0.73	*M. avium* complex 48% *M. xenopi* 25% *M. kansasii* 13%	France	*M. avium* complex 38% *M. gordonae* 29% RGM 16%
UK [28]	Not reported	Not reported	In order of frequency: *M. kansasii* *M. avium* complex *M. malmoense*	UK	RGM 44% *M. avium* complex 22% *M. kansasii* 11%
Australia [6]	2005	3.2	*M. avium* complex 75% RGM 10% *M. kansasii* 7.7%	Australia	*M. avium* complex 71% RGM 15% *M. kansasii* 4%
New Zealand [29]	2004	1.17	*M. avium* complex 83%		
Japan [23]	1981–1984	1.73	*M. avium* complex 75% *M. kansasii* 20%	Asia	*M. avium* complex 54% RGM 31% *M. gordonae* 6%
Taiwan [24]	2000–2012	$13^{\#}$	RGM 44% *M. avium* complex 42% *M. kansasii* 7.1%		
USA [3]	1991–2007	$5.5^{¶}$	*M. avium* complex 80% RGM 18% *M. kansasii* 5.5%	North America	*M. avium* complex 52% RGM 20% *M. gordonae*/*M. xenopi* 12%
Brazil [30]	1996–2005	Not reported	*M. avium* complex 60% RGM 20% *M. gordonae* 8.6%	South America	*M. avium* complex 31% RGM 21% *M. kansasii* 20%

M.: *Mycobacterium*; RGM: rapidly growing mycobacteria. $^{\#}$: in 2012; ¶: prevalence.

NTM species [41]. Only one patient was diagnosed with definite NTM-LD. Moreover, among 126 severe COPD patients undergoing lung volume reduction surgery or bullectomy, 14 (11%) had histological evidence of mycobacterial infection despite lack of clinical and radiological suspicion [42]. A minority of surgical specimens (four out of 14) were sent for mycobacterial tissue culture, and a half of them grew *Mycobacterium xenopi*. The study implicates that subclinical NTM-LD may be present in patients with severe COPD, although its clinical significance remains to be determined [42].

Predisposing factors of NTM pulmonary infection: is COPD one of them?

Findings that NTM are widespread in the environment and NTM pulmonary infection is developing in relatively few people indicate that individual vulnerability matters. Underlying disorders and immunosuppressive status are well-known risk factors of NTM pulmonary infection [43–47]. However, primary lung conditions are also important [36, 48]. With the exception of a prior history of TB or bronchiectasis, COPD is frequently reported as the pre-existing lung condition associated with NTM pulmonary infection [36]. However, prospective cohort studies documenting a causal relationship are still lacking.

There are several hypotheses that attempt to explain why NTM pulmonary infection increases in a host with COPD (figure 1). First, cigarette smoke exposure, the main factor responsible for COPD development, can induce a switch from apoptotic to necrotic cell death in airway epithelium [49], which compromises airway immunity. Given that smoking is known to increase the risk of pulmonary TB [50], it is likely that smoking also increases the risk of NTM-LD. In addition, local airway inflammation of COPD causes mucosa damage and defects in mucus clearance, that are prone to NTM adherence [51] and growth of mycobacteria [52].

ICSs are recommended in patients with moderate-to-severe COPD [53, 54]. However, ICS therapy has been shown to increase the risk of pneumonia in clinical trials [55, 56] and even

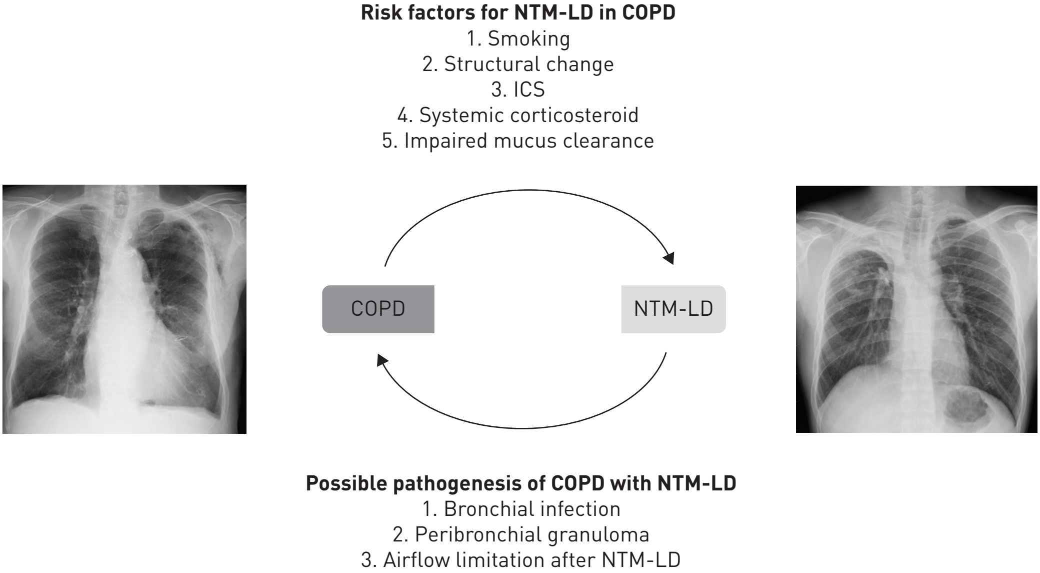
Risk factors for NTM-LD in COPD
1. Smoking
2. Structural change
3. ICS
4. Systemic corticosteroid
5. Impaired mucus clearance
COPD
NTM-LD
Possible pathogenesis of COPD with NTM-LD
1. Bronchial infection
2. Peribronchial granuloma
3. Airflow limitation after NTM-LD

Figure 1. Possible association between COPD and non-tuberculous mycobacteria lung disease (NTM-LD).

increases the risk of pulmonary TB [57, 58]. Moreover, a recent study revealed that the possibility of NTM pulmonary infection increases after ICS use among COPD patients, with the odds ratio paralleling ICS dose, from 28.1 for low-dose ICS therapy to 47.5 for high-dose ICS therapy [36]. The use of oral corticosteroids in COPD patients experiencing acute exacerbations is also an important risk factor for pulmonary infection [57, 59]. Though bias exists in these studies, COPD that requires inhaled or systemic corticosteroid therapy could be considered an underlying pulmonary condition for NTM pulmonary infection [42].

Predisposing factors of COPD: is NTM-LD one of them?

NTM pulmonary infection causes numerous radiographical and histological changes in the lungs. In a study reviewing the pathology and thin-section CT of NTM pulmonary infections, bilateral small nodules (100%), cylindrical bronchiectasis (91%) and branching centrilobular nodular lesions (77%) were the most common CT findings seen in the biopsy sites, regardless of mycobacterial species [60]. All biopsy specimens showed a thickened bronchiolar wall, and bronchiolar and peribronchiolar inflammation. Dilated bronchioles were also identified in 86% of patients and epithelioid granulomas with or without caseation were identified in 32% of patients. Pathological findings of bronchiectasis, bronchiolitis, centrilobular lesions, consolidation, cavitation and nodules were also demonstrated in another analysis of MAC pulmonary infection [61]. In particular, extensive granuloma formation was found throughout the airways, suggesting that bronchiectasis and bronchiolitis are caused by MAC infection. Based on these findings, NTM pulmonary infection is very likely to be a cause of small airway obstruction.

At present, human studies on the causal relationship of COPD and mycobacterial pulmonary infection are mainly retrospective cohort and case–control studies. The most common mycobacterial disease, pulmonary TB, has been reported to be an important risk factor of COPD [62, 63]. Among patients with pulmonary TB identified in the National Health Insurance Research Database of Taiwan, the duration of delay in treatment positively correlated with the subsequent risk of developing COPD [64]. A recent study using the same database, reports that the incidence of COPD is 3.08-fold higher in the NTM cases than in non-NTM controls (21.75 *versus* 6.11 per 1000 person-years) [65]. The adjusted hazard ratio of COPD is 3.57 (95% CI 2.56–4.97) for women and 2.89 (95% CI 2.31–3.61) for men.

A recent study of lung function showed decreased $\mathrm{FEF}_{25–75\%}$ (45.4% predicted) in patients with NTM-LD, suggesting small airway involvement [66]. This finding is similar to that of a report on MAC-LD patients [67]. In a clinical observation in Taiwan, NTM-LD was associated with a greater decline in lung function, especially in patients who were young, male, had bronchiectasis and had a large area of lung involvement [68]. Another cohort study in Taiwan suggested that COPD patients with multiple and single respiratory NTM isolates had a greater annual decline in lung function compared with those without NTM isolate (−79.4±32.8 mL *versus* −61.6±31.9 mL *versus* −56.2±31.5 mL) [39]. The risk of acute exacerbation was also higher in the former two groups than that in the latter (0.82, 0.88 and 0.47 episodes per patient-year, respectively). After controlling for confounders, a greater decline in lung function was also observed in COPD patients with either multiple or single respiratory NTM isolates than in those without.

The findings of these studies suggest that airway inflammation in NTM-LD might be associated with COPD. However, further prospective cohort studies are needed to confirm a causal relationship.

Current diagnostic consensus for NTM-LD

Unlike *M. tuberculosis*, the isolation of NTM from respiratory samples does not necessarily indicate NTM-LD. In order to standardise the definition of NTM-LD, an official statement was published by the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) in 2007 [2]. For a diagnosis of NTM-LD, both clinical and microbiological criteria need to be met. Clinically, patients should have respiratory symptoms and signs consistent with NTM-LD, and radiographical patterns suggesting NTM-LD, preferably HRCT of the chest. In the meantime, all other possible diagnoses must be excluded.

Microbiologically, confirmatory findings require two or more positive cultures from sputum samples, or one or more positive culture(s) from bronchial washing or lavage, or transbronchial or other lung biopsy showing mycobacterial histopathological features in conjunction with a positive NTM culture of any respiratory sample. Nevertheless, even the establishment of NTM-LD does not, *per se*, necessitate the start of anti-NTM therapy. Instead, it is a decision based on pros and cons of therapy for an individual patient.

Diagnostic challenge of NTM-LD in COPD patients

In general, the diagnostic criteria for NTM-LD are applicable to COPD patients. However, fulfilling the clinical criteria specific to NTM-LD is difficult under such circumstances. As the initial case, NTM-LD and COPD share similar symptoms, such as chronic cough, sputum production, fatigue, dyspnoea and weight loss, and radiographical features like bronchiectasis and bronchiolitis signs [2, 69, 70]. Moreover, COPD is characterised by chronic airflow limitation that is usually progressive and its natural history is punctuated with exacerbations. Thus, it is a challenge to exactly ascribe such nonspecific symptoms and imaging findings to NTM-LD or COPD alone.

In this regard, the presence of characteristic imaging changes (*i.e.* an upper lobe fibro-cavitary pattern or multifocal bronchiectasis with clusters of small nodules and cavitation in the middle and lower lung fields) may be a diagnostic aid for NTM-LD [2]. Furthermore, the signs of progression of NTM-LD, such as positive sputum acid-fast smears and quantitative sputum mycobacterial burden, as well as the progressive radiographic abnormalities, may help. Currently, standard guidelines for defining NTM-LD, specifically in COPD patients, have yet to be established.

Treatment for patients with concomitant COPD and NTM-LD

The clinical dilemmas and concerns of managing patients with concomitant COPD and NTM-LD are summarised in table 2. The pros and cons of ICS therapy, macrolide therapy and NTM treatment are discussed in the following sections.

The concerns of using corticosteroids for COPD in NTM-LD patients

The mainstay treatment of COPD includes inhaled bronchodilators with long-acting β_2-agonists and anti-cholinergics, and ICSs [69]. Steroids, either inhaled or oral, are of special concern in the management of COPD patients with concomitant NTM-LD. While ICS therapy is recommended in patients with severe and very severe COPD, and patients

Table 2. Clinical dilemma and concerns of managing patients with concomitant COPD and non-tuberculous mycobacterial lung disease (NTM-LD)

Therapy	Benefit	Risk
ICSs	Reduce exacerbations	Development/deterioration of NTM-LD
Macrolide monotherapy	Reduces exacerbations	Macrolide resistance Adverse reaction
Standard anti-NTM therapy	Improves lung function?	Drug tolerance Adverse reaction (especially macrolide-related arrhythmia)

with frequent exacerbations not adequately controlled by long-acting bronchodilator therapy, long-term oral corticosteroid monotherapy is not recommended [69]. The adverse effect of corticosteroid use generally includes increased risk of infection and fractures [71].

Will ICS therapy in the initial case lead to the development and deterioration of NTM-LD? Several studies reveal an association of ICSs, oral corticosteroids and the risk of TB [57, 72, 73]. For NTM-LD, a retrospective study based on a total of only 14 asthmatic patients with NTM showed that the risk of NTM-LD was higher in asthmatic patients who were older, had more severe airway limitation and received higher ICS doses [74]. Recently, a population-based case–control study in Denmark showed that chronic respiratory disease, particularly COPD treated with ICSs, was a strong risk factor for NTM-LD [36]. The odds ratios for NTM-LD were 29.1 (95% CI 13.3–63.8) for patients with COPD under ICS therapy and 7.6 (95% CI 3.4–16.8) for COPD patients without ICS therapy. The risk of developing NTM-LD in COPD patients parallels the ICS dose and is higher for fluticasone than for budesonide [36]. This study provides the best current evidence that ICS use can contribute to the development of NTM-LD in COPD patients.

The concerns of using macrolides for COPD and bronchiectasis in NTM-LD patients

Macrolides are the cornerstone of treatment for major pulmonary NTM pathogens, including MAC and *Mycobacterium abscessus* [2]. Macrolides also possess anti-inflammatory effects and are being increasingly used in chronic inflammatory airway diseases like CF, COPD, bronchiectasis and asthma [75].

Several studies have shown a modest reduction in AECOPD with macrolides. The largest randomised study included 1142 COPD patients randomly assigned to receive azithromycin or placebo for 1 year in addition to usual care. The result was decreased frequency of exacerbations and improved quality of life in patients taking azithromycin for 1 year [76]. A recent meta-analysis also showed a 37% relative risk reduction in COPD exacerbations among patients taking macrolides compared with those taking placebo [77]. However, an increase in macrolide resistance has been shown in some studies [13, 78]. There are concerns that long-term monotherapy with macrolides will lead to drug resistance in NTM, as in the initial case. A study has shown that previous monotherapy with macrolides is a strong risk factor for subsequent macrolide-resistant MAC [79]. Patients with macrolide-resistant MAC have worse survival and experience progressive disease, as the remaining treatment options are rather limited [79].

Concerns may differ in other pathogens of NTM-LD. *M. abscessus* subspecies *abscessus* have a poor response to macrolide therapy due to their innate macrolide resistance from the *erm* gene [80]. *M. abscessus* subspecies *bolletii* (*M. massiliense*) is thought to differ from *M. abscessus* subspecies *abscessus* due to the inactivating *erm* gene and is susceptible to macrolides [80]. Macrolides are not included in the standard combination regimen for *M. kansasii*. The role of macrolides is primarily second-line therapy reserved for rifampicin-resistant *M. kansasii* [2]. The impact of long-term macrolide therapy on macrolide resistance in *M. abscessus* subspecies *bolletii* (*M. massiliense*) and *M. kansasii*, however, remains to be determined.

There is another emerging issue besides drug resistance in the use of macrolides. Based on the clinical finding that chronic azithromycin use in CF patients is associated with increased infection with NTM, a recent study has shown that azithromycin can block autophagosome clearance by preventing lysosomal acidification, thereby impairing phagosomal degradation in primary human macrophage [81]. This finding raises further concerns about whether chronic use of macrolides, particularly azithromycin, would predispose vulnerable patients to a greater risk of NTM infection.

Does NTM treatment improve lung function in COPD cases?

The adverse impact of NTM on lung function decline has been reported [39, 68]. This has led to the hypothesis that treatment and eradication of NTM will lead to improved lung function. However, few studies have addressed this issue. A previous study focussing on lung function change in 68 patients with NTM-LD, failed to demonstrate that NTM treatment was associated with lung function improvement, perhaps due to the inadequacy of the NTM treatment used [68]. A study with a small case number suggested a beneficial effect of anti-MAC treatment on lung function in MAC patients with abnormal baseline lung function [82]. Further prospective studies are warranted to describe changes in lung function following anti-NTM treatment.

The initiation of anti-NTM therapy should be evaluated individually. As stated in the 2007 ATS guidelines, the decision for NTM treatment should be based on the potential risks and benefits of therapy for individual patients [2]. Since NTM-LD with concomitant COPD has greater disease severity and the potential benefit of improving lung function, a more aggressive attitude towards diagnosis and treatment may be debatable. However, the side-effects and tolerance of anti-NTM therapy should also be considered, especially in elderly COPD patients [83]. Special attention should be paid to the use of macrolides and the risk of cardiac arrhythmias, as heart disease is not uncommon among COPD patients and may contribute to a higher risk of cardiac arrhythmias [84].

Outcome

The outcome of patients with concomitant COPD and NTM-LD is often discussed within the range of lung function, acute exacerbations, respiratory complications and survival. Current evidence suggests that COPD patients with concomitant NTM-LD are at a higher risk of acute exacerbation and have more severe lung function decline; the evidence also suggests that the two diseases might have additive effects on lung function decline [39, 68].

Rather than being life-threatening, NTM-LD is usually an indolent disease that mainly affects the patient's quality of life. Recent studies have shown that mortality from NTM-LD is increasing [85, 86]. The reason is unclear, although strengthened awareness and knowledge of the disease among physicians, as well as improved laboratory techniques, may have contributed [85]. When discussing the mortality of NTM-LD, COPD is often included as one of the comorbidities [86]. Patients with NTM-LD have been shown to be at a high risk of respiratory failure, especially those with comorbid COPD [87]. The adverse impact of NTM colonisation/infection on the survival of COPD patients remains hypothetical and warrants more direct evidence. As NTM will lead to greater lung function decline in COPD patients, concomitant COPD/NTM-LD is likely to have a worse outcome.

Conclusion

The incidences of COPD and NTM-LD are increasing, although the two may act in collusion. As their symptoms and signs are nonspecific, definite diagnosis of NTM-LD in COPD patients remains challenging and standard guidelines have yet to be established. Although they are beneficial to COPD management, ICS and macrolide therapy may be harmful to NTM-LD. Starting anti-NTM therapy should be based on the potential risks and benefits of therapy for individual patients. As NTM pulmonary infection may lead to more severe lung function decline and AECOPD, a more aggressive attitude towards diagnosis and treatment may be necessary.

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Pneumonia or exacerbation of COPD?

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Case history: A 55-year-old obese woman presents with dyspnoea, increased production of green sputum, and low-grade fever. She has smoked for 35 years, one pack every day. A chest radiograph is equivocal for a new pulmonary infiltrate, due to her body habitus. What is the most likely diagnosis: acute pneumonia or an exacerbation of COPD?

Chapter summary: From a clinical perspective, the distinction between pneumonia and exacerbations of COPD can be challenging. Chest radiography is often required to make the distinction, but its findings may be obscured by pre-existing conditions. Biomarkers have shown the most promise: both CRP and procalcitonin can reliably distinguish between COPD exacerbations and pneumonia, but further studies are required to make final recommendations on their use. Specific and distinctive inflammatory patterns in both pneumonia with concurrent COPD and exacerbations of COPD have been typified. Although they share some similarities, the cytokine profiles and macrophage activation are different in these conditions. Inhaled steroids are used widely in COPD and are associated with an increased risk for pneumonia but not for mortality, suggesting multiple underlying mechanisms.

When a patient with a history of COPD has an acute worsening of respiratory symptoms, the clinician is presented with a diagnostic dilemma: is this pneumonia or an exacerbation of COPD? Despite other diagnostic possibilities, such as pulmonary embolism or congestive heart failure, careful attention should be directed to COPD exacerbations and pneumonia, which are more frequent events in these patients and have the highest morbidity [1, 2]. Interestingly, there is evidence that both conditions may influence each other, affecting patient outcomes. Both conditions are characterised by increased inflammation, both locally and systemically [3]. Although COPD exacerbations and pneumonia may partially share pathophysiological features, the treatment, management and prognosis vary significantly. For these reasons, it is important to reach an accurate diagnosis.

Clinical similarities and differences

From the clinical perspective, COPD exacerbations and pneumonias may be difficult to differentiate (table 1). Both pneumonia and an exacerbation of COPD cause worsening of

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Table 1. Clinical characteristics of pneumonia and COPD *versus* COPD exacerbations

Clinical characteristics	COPD plus pneumonia	COPD exacerbation
Fever	+	+/–
Chills	+	+/–
Purulent sputum	++	+
Increased sputum	++	++
Pleuritic chest pain	+	+/–
Wheezing	+/–	+
Dyspnoea	++	++
Cough	++	++
WBC elevation	++	+

WBC: white blood cell.

respiratory symptoms. These tend to appear acutely or subacutely, and are characterised by dyspnoea, cough, increased sputum production and presence of purulent sputum. Systemic symptoms are frequent and include malaise, fatigue, fever and decreased appetite. Although pneumonia may have objective findings on physical examination and chest radiography, the diagnosis is often based on the presence of subjective clinical features, such as cough, fever, sputum production and pleuritic chest pain [4, 5]. The definition of a COPD exacerbation also relies on subjective findings: a difference from the day-to-day variation in the respiratory symptoms that requires a change in treatment [6]. The subjective manner by which the diagnosis is achieved makes the differentiation of these two conditions difficult. To complicate matters further, pulmonary infiltrates on chest radiography may be difficult to detect in patients with underlying chronic lung disease, obesity or other coexisting diagnoses [7]. Additionally, in subgroups of patients, such as the elderly, the symptoms of both of these conditions might be vague or equivocal [8].

There are still some differences and diagnostic tools that may aid the clinician in the diagnosis. Wheezing may be a prominent complaint or clinical observation that would make the diagnosis of COPD exacerbation more likely. Despite these signs suggesting a COPD exacerbation, patients with COPD and pneumonia may still present with bronchospasm. Based on previous events, patients may be able to distinguish for themselves whether they are having an exacerbation of COPD [9]. In contrast, a chest radiograph may reveal pulmonary infiltrates or a consolidation that would confirm the diagnosis of pneumonia [5, 7]. Chest CT, which is now widely available and often used to evaluate for other potential diagnoses (*e.g.* pulmonary embolism), may also reveal pulmonary infiltrates or consolidations that would not readily be apparent on chest radiography.

Biomarkers

Beyond the clinical markers and cues, can we use biomarkers to distinguish between pneumonia and an exacerbation of COPD? Because COPD exacerbations and pneumonia have specific inflammatory patterns, it is reasonable to predict that biomarkers may be useful to aid in the diagnosis. This is of particular importance, as it could reduce the unnecessary use of antibiotics and potentially reduce drug-resistant bacteria. For example, guidance by serum procalcitonin levels, which are raised during bacterial infections, has led to substantially reduced use of antibiotics in patients with acute respiratory symptoms, including those with COPD [10–12]. Other studies have validated these findings [13, 14]. Importantly, in these studies, withholding antibiotics did not compromise outcomes. CRP, a biomarker of active inflammation, has also been used to evaluate patients with pneumonia. A study that included patients with pneumonia and asthma or COPD exacerbations showed that the combined use of procalcitonin and CRP could reliably distinguish pneumonia from asthma or COPD [15]. Another study also demonstrated higher levels of procalcitonin and CRP, but not neopterin, in patients with COPD with concurrent pneumonia compared with those with stable or exacerbated disease [16]. Thus, evidence exists that both procalcitonin and CRP may be reliably used to identify the need for antibiotics in COPD. Current guidelines do not yet advocate the widespread use of these biomarkers routinely during the evaluation of exacerbations [6]. Future studies are needed to confirm prospectively the utility of these assays.

Infections and their influence on COPD exacerbations

Viral infections

Despite significant seasonal variation in prevalence of viral infections, up to 60% of these have been linked to COPD exacerbations [17, 18]. Rhinoviruses, coronaviruses, influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, picornavirus and human metapneumovirus have been associated with exacerbated COPD. COPD exacerbations associated with viral infections have an increased risk of requiring a hospitalisation and often require longer recovery periods after resolution of the acute phase of disease [19–21]. Beyond the direct effect of viral infection on airway epithelium, there may be other more subtle changes through alterations of the pulmonary inflammatory patterns and microbiome. For example, after intentional infection with rhinovirus, patients with COPD experienced a six-fold increase in sputum bacterial RNA copy number (particularly involving *Haemophilus influenzae*), a change that was still evident 42 days after initial infection [22]. This was not observed after intentional RSV infection in healthy controls. This two-hit phenomenon may explain some components of the pathogenesis of disease in viral exacerbations of COPD.

Seasonal, geographical and other environmental factors, as well as the availability of diagnostic testing, dramatically affect the prevalence of viral infections. No evidence exists to suggest a benefit of specific antiviral therapy for viral infections in patients with obstructive lung disease and current guidelines do not include the use of antivirals for COPD exacerbations.

Bacterial infections

Bacteria directly implicated with COPD exacerbations include *H. influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*. Other bacteria have been isolated in the sputum of COPD patients, such as *Staphylococcus aureus* and enteric Gram-negative pathogens, but these organisms may represent the intrinsic microbiota of COPD-diseased airways. Based on consistently negative culture results, the lower airways have long been considered sterile. In the past decade, however, advanced DNA-based techniques have demonstrated a complex microbial milieu in the lower airways of normal patients [23]. This microbiological environment certainly seems associated with immunological influences on airway function. Much active research is aimed at defining the microbiome of the lung in health and disease. Early studies in this area have demonstrated that the pathogenic makeup of the lower airways in patients with COPD differs from that of nondiseased individuals and is not consistent across Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages [24]. Particularly in severe disease, the airways of COPD patients have a myriad of potential pathogens [25]. Colonisation of the airways may thus lead to specific host–pathogen interactions that may enable or predispose exacerbations. Indeed, various inflammatory markers, including TNF-α, IL-6, IL-8 and neutrophil-derived cytokines, are consistently elevated in COPD patients in a manner consistent with this hypothesis [26–28].

The precise mechanism of how bacteria may elicit a COPD exacerbation has only been partially elucidated. When a patient acquires a new bacterial strain, pathogenic virulence combines with the host lung's defence mechanisms to effect a change in airway and systemic inflammation. The subsequent response can be strain specific and may lead to increased respiratory and systemic symptoms, which develop into an exacerbation. This mechanism is supported by evidence from studies that show an increased risk of developing a COPD exacerbation after acquisition of a new bacterial strain [29]. Exposure to new bacterial strains can generate a more intense neutrophilic inflammation and an increased inflammatory marker profile compared with exposure to pre-existing strains [30]. Further illustrating this concept, evidence suggests that bacterial strains identified during COPD exacerbations are more closely associated with pronounced airway inflammation than those regarded as "airway colonisers" [31]. One may conclude from this evidence that different strains may lead to variable host responses and that newer strain exposures may have the most impact on airway function. In a prospective, longitudinal cohort of COPD patients, the acquisition of new bacteria strains (particularly *H. influenzae*, *S. pneumoniae*, *M. catarrhalis* and *P. aeruginosa*) was associated with both systemic inflammation and an intense neutrophilic response in the airway [30]. Therefore, the microbial burden in the lungs of patients with COPD probably represents a complex immunological environment whose balance potentially affects the development of exacerbations.

Host factors

Why is it that when patients with COPD are exposed to bacteria (*e.g. S. pneumoniae*) some develop pneumonia while others have an exacerbation of COPD? Few studies have prospectively evaluated this question. HUERTA *et al.* [32] prospectively studied 249 COPD patients admitted to hospital either for pneumonia or an exacerbation. Patients with pneumonia, at days 1 and 3, showed a more powerful biological signalling, as evidenced by significantly higher levels of CRP, procalcitonin, TNF-α, IL-1, IL-6 and IL-8, compared with those with an exacerbation. This inflammatory pattern was confirmed in further analyses, even after correction for disease severity and therapy with ICSs [32]. Additionally, in this cohort, patients with COPD and pneumonia tended to have more systemic symptoms and presented with severe sepsis and septic shock more often than those with exacerbations [32]. Inflammatory markers were not measured at baseline (before the respiratory event developed), so it is difficult to identify a possible *a priori* susceptibility to pneumonia. Nevertheless, among the patients with COPD, there might be specific inflammatory patterns that affect the risk for infection and other outcomes. For example, a study showed that higher baseline counts of white blood cells and levels of CRP, IL-6, IL-8, fibrinogen and TNF-α were associated with increased exacerbation frequency and mortality [33]. Other studies have reported similar findings [34, 35].

It is known that as the severity (based on FEV1) of COPD increases, exacerbations become more frequent [36]. Similarly, the risk for a hospitalisation due to pneumonia increases as COPD (based on FEV1) progresses [37]. Interestingly, the study by Huerta *et al.* [32] showed that patients with COPD and pneumonia had significantly higher FEV1 values compared with those having an exacerbation (1.44±0.5 L *versus* 1.30±0.6 L, respectively). The reason for these observations is not readily understood, but it is possible that pneumonia may affect susceptible hosts at earlier stages of the disease compared with exacerbations. Other studies have not shown this difference, but this an area of ongoing research [38].

Macrophage activation has also been found to be different in COPD patients with pneumonia compared with those with COPD exacerbations. Activated macrophages can be classified into two groups based on their phenotype and function. M1 describes those macrophages that promote inflammation and extracellular matrix destruction and have bactericidal activities [39]. Conversely, M2 macrophages inhibit the inflammatory response and promote tissue regeneration and angiogenesis [39]. A study evaluated the macrophage phenotypes observed in the sputum of three distinct groups of patients with the following diagnoses: pneumonia, COPD exacerbations, and pneumonia plus COPD [40]. In patients with only pneumonia, the macrophages exhibited an M1 phenotype, while those with a COPD exacerbation had an M2 phenotype. Interestingly, patients with coexisting pneumonia and COPD did not have a clear distinction of M1 or M2. This suggests that specific cellular lines may be affected differently during pneumonia or COPD exacerbations, which in turn affect the microenvironment of the lung.

Finally, another important observation is that microbiological patterns seem to differ among groups. For instance, *H. influenzae* appears to be more commonly isolated in COPD patients with an exacerbation, and *S. pneumoniae* is more frequent in those with COPD and pneumonia [32, 41–44]. Perhaps different pathogens affect the inflammatory cascade in such a way as to predispose a patient to develop an exacerbation or a parenchymal infection. Therefore, it is plausible that different inflammatory patterns may predispose patients to develop either pneumonia or exacerbations. This could explain phenotypically why patients with COPD and pneumonia often have more prior episodes of pneumonia and those with COPD exacerbations may have frequent exacerbations [32, 36].

COPD as a risk factor for pneumonia

Risk factors for hospitalisation for pneumonia include age >65 years, male sex, congestive heart failure, liver disease and advanced COPD [45, 46]. One could anticipate that changes in the architecture of lung parenchyma and airways would affect the normal defence mechanisms and predispose patients with COPD to infections, and this is partially supported by the high prevalence of pneumonia in patients with COPD [37, 47]. These changes include increased mucus production, decreased mucus clearance and increased local and systemic inflammation, among others. Patients with advanced COPD are typically older, have poor nutritional status, and are more likely to have other comorbidities, which may also partly increase the risk for infections.

Studies have shown that subjects who have both COPD and pneumonia have worse outcomes compared with similar matched patients without pneumonia with regard to severity of the disease, healthcare utilisation and mortality [48, 49]. COPD has been identified as an independent risk factor for 30-day mortality in patients with pneumonia [50, 51]. Likewise, for those patients that require admission to the intensive care unit for pneumonia, the presence of COPD was associated with higher mortality and need for mechanical ventilation [52]. In contrast, other studies have not shown this association [41, 53–56]. In fact, a study showed that despite COPD patients having more severe pneumonia at admission based on severity scores, the 30-day mortality was similar to patients with pneumonia and no COPD [55]. Similarly, another study revealed that, although patients with COPD had a more severe clinical presentation and longer hospital stays compared with patients without COPD, a difference in mortality rates was not observed [56]. The reasons for the discrepancies in the results of these studies are multifactorial. A recent systematic review explored the risk of death with concomitant pneumonia and COPD compared with pneumonia or COPD exacerbation alone. There was considerable heterogeneity in the studies evaluated and a nonsignificant mortality risk was found in patients who had both pneumonia and COPD [57]. There were limitations in some of these studies, in that the definition of COPD did not always include spirometric findings. This not only potentially misclassified patients as having COPD, but also the severity of COPD (*i.e.* based on $\mathrm{FEV_1}$) could not be determined. Another potential confounder is that patients with known COPD may be treated differently during an acute respiratory illness in different healthcare settings (*i.e.* early use of antibiotics) and may have different vaccination patterns. Others may also be affected by chronic treatment with inhaled or systemic corticosteroids, which in turn may affect the host's defence mechanisms.

In summary, controversy remains regarding the role of COPD as a risk factor for pneumonia. Larger, prospective studies are still required to clarify this issue. Nevertheless, clinicians should continue to pay close attention to COPD patients with signs of pneumonia, especially those with advanced disease, because of their potentially worse outcomes.

ICSs and the risk of pneumonia

ICSs are commonly used for stable COPD. Multiple studies have evaluated the impact of ICSs on various COPD outcomes. A recent systematic review evaluated the outcomes of 55 trials, including 16 154 patients who received ICSs for COPD [58]. This review demonstrated no benefit in the decline in $\mathrm{FEV_1}$, but showed an improvement in the rate of decline in quality of life and rate of exacerbations. Several studies have not shown an improvement in COPD mortality with ICS therapy, but a relatively high dropout rate may have affected the overall analyses [59, 60]. This is due to the fact that patients with more severe disease (with an expected higher mortality) tended to dropout from the placebo arms, instead seeking therapy. The systematic review by Yang *et al.* [58] also did not show a significant effect on mortality in COPD patients receiving ICSs (OR 0.98, 95% CI 0.83–1.16, n=8390 patients).

ICSs have been associated with adverse reactions and unintended effects [61]. The association of ICSs and pneumonia in COPD patients has been studied extensively in various studies. A systematic review that included 43 studies (26 studies with fluticasone, 17 studies with budesonide) recently analysed the effects of ICSs on the risk of pneumonia [62]. Both fluticasone (OR 1.78, 95% CI 1.50–2.12) and budesonide (OR 1.62, 95% CI 1.00–2.62) increased nonfatal serious adverse pneumonia events compared with placebo. There was no significant difference in overall mortality rates with either medication. This observation has been reported by other reviews [63]. Conversely, after adjusting for confounders, a meta-analysis that evaluated specifically budesonide did not find an increased risk for pneumonia [64]. Although they bind to the same glucocorticoid receptor, each type of ICS may have different effects due to their specific chemical composition. For

Table 2. Phenotypic characteristics of pneumonia and COPD *versus* COPD exacerbations

	COPD plus pneumonia	COPD exacerbation
Previous respiratory events [32]	History of previous pneumonias	History of previous COPD exacerbations
Bacterial pathogen most commonly isolated [32, 41–44]	*Streptococcus pneumoniae*	*Haemophilus influenzae*
Blood cell counts [15, 32]		
Leukocytes	↑↑↑	↑↑
Neutrophils	↑↑	↑
Macrophage phenotype [40]	M1+M2	M2
Cytokines [32]		
IL-1	↑	↑
IL-6	↑↑↑	↑
IL-8	↑	↑/–
IL-10	–	–
TNF-α	↑↑↑	↑↑
Biomarkers [16, 32]		
CRP	↑↑↑	↑↑
Procalcitonin	↑	–
Neopterin	↑	↑
Pathological features [74–77]	Alveolar spaces uniformly filled with an exudate rich in fibrin, with bacteria, leukocytes, macrophages and erythrocytes Alveolar walls are thickened with capillary congestion and oedema	Alveolar spaces irregularly filled with mucinous material and leukocytes, lymphocytes, macrophages and eosinophils Bronchiolar wall inflammatory cell infiltration

↑, ↑↑, ↑↑↑: increased levels; –: unchanged level.

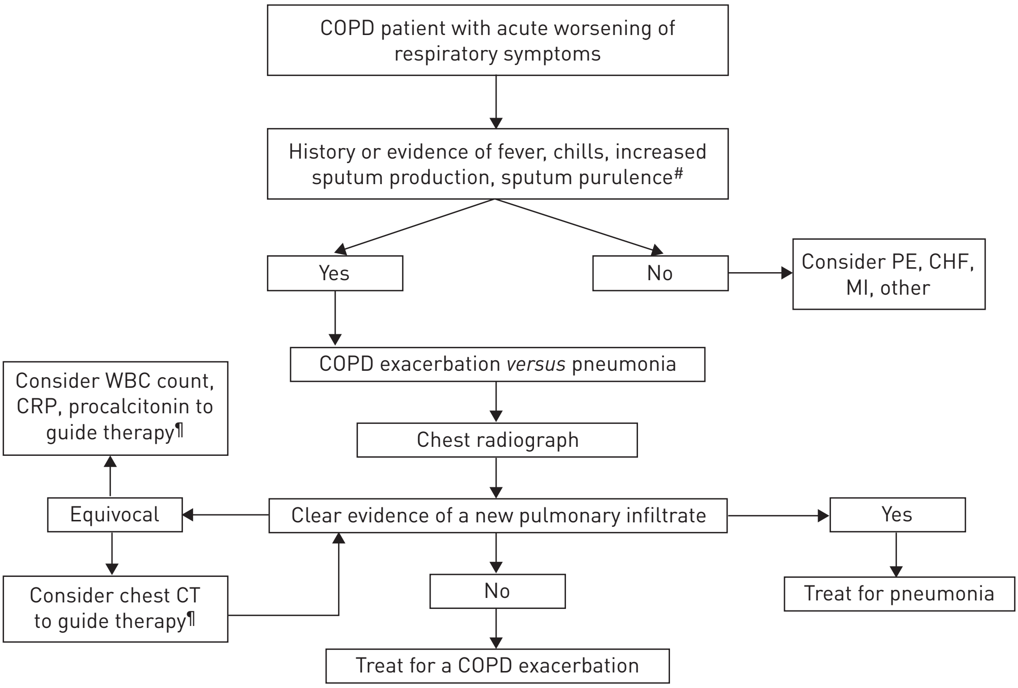
COPD patient with acute worsening of respiratory symptoms
History or evidence of fever, chills, increased sputum production, sputum purulence#
Yes
No
Consider PE, CHF, MI, other
COPD exacerbation versus pneumonia
Consider WBC count, CRP, procalcitonin to guide therapy¶
Chest radiograph
Equivocal
Clear evidence of a new pulmonary infiltrate
Yes
Consider chest CT to guide therapy¶
No
Treat for pneumonia
Treat for a COPD exacerbation

Figure 1. Diagnostic algorithm for COPD patients with pneumonia *versus* exacerbations of COPD. PE: pulmonary embolism; CHF: congestive heart failure; MI: myocardial infarction; WBC: white blood cell. #: elderly patients may have decreased intensity of symptoms; ¶: if the patient requires admission to the intensive care unit or is hypoxic, antibiotics should not be delayed.

instance, it has been shown that budesonide and fluticasone may have different serum concentrations depending on airway calibre [65]. It is possible that the unique pharmacokinetic properties of the different ICSs may result in different risks for pneumonia.

If there is an increased risk for pneumonia with the use of ICSs, why are the mortality rates not affected? The answer is not readily apparent. The rationale for the increased risk for pneumonia in COPD patients is the immunosuppressive effects of ICSs. This is supported by the observation that the dose of ICSs is directly proportional to the risk of pneumonia [66]. Nevertheless, corticosteroids are potent anti-inflammatory medications that attenuate pro-inflammatory mediators that potentially could reduce the severity of pneumonia in patients with pre-existing COPD. The beneficial effects of corticosteroids in COPD are well documented. Studies have shown that treatment with systemic corticosteroids for exacerbations of COPD reduces the likelihood of failure in treatment, decreases relapses and shortens the length of stay in hospital [67–69]. Even shorter courses of systemic corticosteroids have showed improved outcomes in COPD [70]. Interestingly, recent studies have revealed that adjunctive treatment with systemic corticosteroids improved outcomes in patients with severe pneumonia [71, 72]. Thus, it is possible that ICSs, although less potent than systemic corticosteroids, may have a double effect on the risk and outcomes of pneumonia in COPD patients. Further studies are needed to clarify the potentially protective role of ICSs on pneumonia in COPD.

For these reasons, clinicians should consider therapy with ICSs in COPD patients carefully. Controversy exists regarding the number needed to treat to prevent an exacerbation and the number needed to treat to induce pneumonia [59, 73]. Therefore, a careful risk/benefit analysis and discussion should be carried out by clinicians and patients to address the improvement in quality of life and decreased exacerbations *versus* the increased risk of developing pneumonia and other side-effects with the use of ICSs.

Conclusion

From a clinical perspective, the distinction between pneumonia in COPD patients and exacerbations of COPD can be challenging. Although chest radiography may assist in the distinction of these conditions, other coexisting conditions may often affect the sensitivity and specificity of this test. Other imaging modalities, such as CT, can more reliably differentiate between these conditions, but their cost and availability may be prohibitive. Despite this, there are specific phenotypic differences between patients with pneumonia with COPD and exacerbations of COPD (table 2). Biomarkers have shown the most promise; both CRP and procalcitonin can reliably distinguish between COPD exacerbations and pneumonia. These tests may be considered in diagnostic algorithms for the workup of COPD patients with an acute deterioration of their respiratory condition (figure 1). However, further studies are required to make definitive recommendations regarding their widespread use. Studies have demonstrated several differences in the inflammatory patterns of pneumonia with concurrent COPD and exacerbations of COPD. These studies may serve as a foundation for further studies evaluating diagnostic algorithms that include measurement of cytokines and other biomarkers.

Although ICSs are associated with an increased risk for pneumonia, this therapy has not been associated with increased mortality. This suggests that ICSs may have a double effect, but future studies are needed to elucidate the precise mechanisms of these observations. Our understanding of how pneumonia and COPD influence each other has increased greatly over the past decade, but future studies are needed to further determine how to better distinguish between these conditions, in order to provide the most appropriate therapy.

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Prophylactic antibiotics

David J. Serisier[1,2,†]

Case history: A 65-year-old male ex-smoker with COPD and moderately-severe airways obstruction (FEV1 48% predicted) presents with an exacerbation which is successfully managed with short-course, outpatient oral amoxicillin and prednisone. He has not had any other exacerbations in the past 12 months. You wonder whether he should be prescribed maintenance prophylactic azithromycin.

Chapter summary: Convincing data supporting the use of typical antibacterial agents as prophylaxis for infective exacerbations of COPD are lacking, in spite of the apparent importance of bacterial infection in these episodes. Only macrolide antibiotics have shown consistent benefits on exacerbation prevention, although perhaps not primarily by a traditional antibacterial mechanism.

There does not appear to be any net increased cardiovascular risk with macrolides when used for appropriate clinical indications, at least for azithromycin. Arguably the greatest risks relate to the use of these agents in COPD are microbiological, as widespread use will promote further increases in population bacterial resistance. Additionally, recent data reveal that prophylactic macrolide therapy fosters a shift in respiratory microbiota composition towards communities with more antibiotic resistant bacteria particularly *Pseudomonas aeruginosa*.

Achieving an appropriate balance of risk–benefit with macrolide antibiotics can be realised by limiting their use to COPD patients at high risk of hospitalisation, and by preferentially using less potent (low-dose erythromycin) over potent, long-acting (azithromycin) macrolides.

Maintenance antibiotic prophylaxis in COPD or "chronic bronchitis" has long been a controversial topic in airways disease. Given that AECOPD have the potential for significant morbidity, healthcare-associated costs [1] and mortality [2], any intervention that reduces their frequency and/or severity clearly merits consideration. Infection is implicated in the majority of these episodes [3], and antibacterial prophylaxis therefore represents a logical therapeutic approach. However, only macrolide antibiotics have convincingly demonstrated benefits in COPD, implying a mechanism of effect that is not traditionally antibacterial and challenging our current understanding of the role of bacterial infection in AECOPD.

This chapter will review the literature relating to the rationale for antibiotic prophylaxis in COPD, evidence for the efficacy of antibiotic prophylaxis and the potential risks of these

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agents. For the purposes of this chapter, "COPD" refers to smoking-related COPD and will not consider other conditions such as bronchiectasis.

I hope to convince readers that the rationale for antibiotic prophylaxis (including our understanding of the role of bacterial infection in AECOPD) remains overly simplistic, that we should focus attention upon strategies to prevent community antimicrobial resistance related to their use (rather than obfuscating this by debating its inevitable occurrence) and therefore that our approach to the use of this treatment paradigm must be thoughtful, restrained and targeted.

Prophylactic antibiotics in COPD; does the rationale stack up?

The rationale for the use of prophylactic antibiotics in COPD is predicated upon two key arguments that firstly propose a compelling pathophysiological basis for a likely mechanism of benefit (*i.e.* acute bacterial infection is a critical driver of these episodes), and that secondly justify the use of antibiotics on the basis of averting outcomes of sizeable magnitude (*i.e.* AECOPD have significant consequences that warrant risking the development of bacterial resistance). However, the available data, presented in the following sections, should challenge both of these contentions.

The importance of AECOPD

Diminishing the frequency and/or impact of AECOPD that require hospitalisation is undoubtedly of value to both the patient and the healthcare system; these episodes present significant risks of mortality [2], subsequent deterioration in patient performance and quality of life (QoL) and are costly to the healthcare system [1]. However, for exacerbations that can be successfully managed as an outpatient, particularly if they do not have economic or societal costs substantially in excess of their occurrence in a non-COPD population, the benefits of preventive therapies are debatable.

While outpatient AECOPD have impacts upon quality of life [4, 5] and perhaps also upon work days, subjects without any significant underlying lung disease experience similar impacts from episodes of "exacerbation" that are likely to predominantly reflect simple viral upper respiratory tract infection or acute bronchitis [6]. Arguing for the continuous, maintenance use of antibiotic prophylaxis for prevention of exacerbation-like episodes in all members of the community on the basis of reducing days off work would be ridiculous and even the acute use of antibiotics to treat these episodes is clearly inappropriate. Furthermore >80% of patients with mild–moderate COPD recover from AECOPD without the need for even acute antibiotics [7]. Hence, for many patients experiencing AECOPD, neither acute nor prophylactic antibiotic therapy is appropriate.

The additional argument for prophylactic antibiotics in COPD contends that there are permanent sequelae following resolution of the exacerbation, specifically accelerated decline in lung function. However published data do not suggest a sizeable effect of AECOPD on lung function decline, except in current smokers [8]. Of the largest and longest studies evaluating this issue, three found no significant evidence of an effect of exacerbations upon FEV_1 decline [9–11], except in current smokers (but not quitters) in the largest study [12]. In the most recent study [13], AECOPD were shown to have a statistically significant effect on rate of decline of FEV1, although the effect was small (additional 2 mL·year^{-1} per exacerbation) [14].

The role of acute airway bacterial infection in AECOPD

Most AECOPD are considered to be related to acute airway infection [15–17], although determining the relative importance of bacterial infection in the pathogenesis of AECOPD with any degree of certainty is no easy task. Studies to date have been hindered by the nature of the patient populations studied (and whether they accurately reflect the broader COPD population), including lack of adequate exclusion of other clinical conditions and small, select populations for what is a heterogeneous disease. Additionally, most studies have relied on culture-dependent analysis and the identification of specific PPMs. However, the simple detection of bacteria by culture does not indicate new infection, and culture-independent molecular techniques in several diseases have shown significant differences between the results of culture and the entire pool of bacteria present within respiratory secretions [18–20]. Even studies simply evaluating the potential role of increased bacterial load in AECOPD have come to directly opposing conclusions [21–23]. In subjects with chronic bronchitis, a proportion of exacerbations coincided with the acquisition of a new strain of bacterial pathogen, although in two-thirds of cases where a new strain was identified there was no exacerbation [24]. There are few data investigating airway microbial community composition (using culture-independent methods) at AECOPD, although a recent small study did not show any significant change in bacterial community composition at exacerbation [25].

In AECOPD in which an infecting organism is found in sputum, viruses and bacteria (PPMs by culture) are each detected in roughly half of cases [17]. Two case–control studies have found significantly higher rates of detection of viruses in respiratory secretions during AECOPD compared with stable COPD (37% *versus* 12%, 56% *versus* 19%) [26, 27]. Finally, an experimental human rhinovirus infection of AECOPD [28] was associated with secondary bacterial airway infection in 60% of subjects [21], resulted in significant increases in total bacterial load [29] and was accompanied by evidence of increased proteobacteria sequences (particularly *H. influenzae*) but without significant changes in bacterial community composition [29].

Rationale for prophylactic antibacterial agents in COPD: a summary

While hospitalised AECOPD is an outcome clearly worthy of preventive efforts even where there may be risks associated with the prophylaxis, many outpatient episodes are not. Furthermore, while acute bacterial infection may be a central driver of AECOPD, the evidence for this is not compelling. Hence, neither the rationale for the potential mechanism of benefit of antibiotic prophylaxis, nor the underlying justification for its broad-based application are supported by robust data.

Antibiotic prophylaxis of AECOPD

Inhaled antibiotics

Antibiotic delivery by inhalation offers an appealing method for antibiotic delivery that minimises risks of systemic side effects while optimising delivery directly to the airway, and prophylactic inhaled antibiotic use is now one of the fundamental pillars of therapy in CF

[30]. Unfortunately, translation of this paradigm beyond CF has been unsuccessful so far, with double-blind randomised controlled trial (RCT) evidence of exacerbation reduction in other airways diseases limited to a single, small phase 2 study in non-CF bronchiectasis [31]. There have been no published studies evaluating prophylactic inhaled antibiotics for exacerbation prevention in COPD. However, levofloxacin for inhalation (MP-376) has been tested in a 48 week, double-blind, randomised, placebo-controlled study, delivered twice-daily by e-flow nebuliser for 5 days of each 28-day treatment cycle, in 322 COPD subjects with at least two exacerbations in the prior year [32]. MP-376 had no effect on exacerbation rate (OR 1.09, 90% CI 0.86–1.39).

Oral antibiotics

Studies evaluating the impact of oral antibiotic prophylaxis on outcomes in COPD are split into 2 distinct time-periods and hence uncertainty around the applicability of studies from the earlier time-period to the modern COPD patient population. A 2013 systematic review identified 19 placebo-controlled RCT's involving a total of 3932 subjects with COPD and/or chronic bronchitis [33]. Due to significant clinical and methodological heterogeneity between trials before 1987 (chronic bronchitis) and the more recent studies (COPD), analyses were separated into two groups according to these time periods. Significant effects of prophylactic antibiotic treatment were found upon exacerbations in both COPD (four macrolide studies, one quinolone; rate of exacerbations RR 0.73, 95% CI 0.66–0.82) and chronic bronchitis (proportion of patients with exacerbation RR 0.93; 95% CI 0.87–0.99). Subgroup analysis in the COPD population according to antibiotic regimen found a significant benefit of macrolides but not quinolones.

Studies in chronic bronchitis

A Cochrane review of studies performed before 1990 (all but one before 1970) identified nine randomised, double-blind, placebo-controlled trials in 1055 subjects with chronic bronchitis; it is likely that many of these subjects had COPD. This review reported marginally fewer treated subjects experiencing any exacerbation (RR 0.91, 95% CI 0.84–0.99) but no significant reduction in the annual exacerbation rate per patient (WMD −0.15, 95% CI −0.34–0.04) [34]. Many of the studies had methodological issues including COPD diagnostic criteria, incomplete reporting and small sample sizes [35–40]. The study durations ranged from 3 months to 5 years and tested a range of antibiotics *versus* placebo, only during winter months. None of the three largest studies (>130 subjects for each) demonstrated significant reductions in acute exacerbations with antibiotics, although two showed reductions in days off work in British working men [41–43]. The largest study randomised 497 men with chronic bronchitis to daily oxytetracline for 7 months of each year, and showed no significant effect on exacerbations of up to 5 years of prophylaxis [41].

Four additional randomised, double-blind, placebo-controlled trials apparently not captured by the Cochrane review, all evaluated once-weekly sulfonamides in chronic bronchitis [44–47]. These studies lasted for between 3 and 12 months, with three carried out across winter only. Three of the studies were small, enrolling fewer than 60 patients each, with two reporting significant reductions in acute exacerbations. In the largest study (n=218) [46], weekly sulfametopyrazine given for 20 weeks across winter significantly reduced the frequency of respiratory illnesses (0.83 *versus* 1.43 per patient) and days off work.

Studies in COPD

Since 2000, there have been a number of studies evaluating maintenance prophylactic antibiotic therapy in COPD, almost exclusively with macrolides. A 2013 Cochrane review of studies in which participants met the definition for COPD identified seven RCTs (although three were excluded) of 3170 patients, with all studies published after 2000 [48]. The proportion of subjects experiencing exacerbation was significantly reduced with continuous macrolide administration for between 3 and 36 months (three studies, n=1262; OR 0.55, 95% CI 0.0.39–0.77), but not with 48 weeks of pulsed moxifloxacin (one study, n=1962; OR 0.87, 95% CI 0.39–1.09), and test for interaction confirmed a significantly greater effect of continuous macrolides than pulsed moxifloxacin. Antibiotics improved QoL overall (WMD −1.78, 95% CI −2.95 to −0.61), although this was based on only two studies [49, 50] and the effect was driven primarily by the study from Albert *et al.* [49]. Two 2013 meta-analyses of six RCTs (n=1485) of macrolides in COPD [51, 52] reported similar, significant reductions in exacerbation rates with macrolides administered for between 3 and 12 months (RR 0.63, 95% CI 0.45–0.87 [51]; and RR 0.62, 0.43–0.89 [52]). One of these studies reported a significant benefit of erythromycin but not azithromycin in subgroup analysis according to specific macrolide [52]; however, this is highly doubtful given the significant effect of azithromycin seen in the largest study of macrolides performed [49].

Macrolides

There have now been eight RCTs published evaluating prophylactic macrolide therapy for exacerbation prevention in COPD [49, 53–59], five of which were placebo-controlled and double-blind. The remaining three studies will not be discussed further here, although each showed significant reductions in both pulmonary exacerbations and hospitalisations with prophylactic erythromycin [54] or azithromycin [53, 55].

In the only "negative" RCT of macrolide therapy in COPD [56], performed in 67 subjects (mean FEV_1 43% predicted, ~50% current smokers, no baseline exacerbation history) clarithromycin given for 3 months had no significant effect on QoL or acute exacerbations compared with placebo. Of the published RCTs, this was the only one to assess clarithromycin, was the shortest, and only seven exacerbations were recorded.

He *et al.* [58] evaluated the effect of erythromycin (125 mg three times per day) upon airway inflammation in induced sputum samples in 36 COPD subjects (FEV_1 43% pred, current smoking not reported, exacerbation history not reported) over 6 months. Surprisingly, in spite of the small sample size (n=15 placebo and 16 erythromycin completed), statistically significant improvements in sputum neutrophils, sputum neutrophil elastase concentration, exacerbation frequency (mean 0.61 *versus* 1.11 per patient) and time to exacerbation (155 *versus* 86 days) were reported with erythromycin.

In the second double-blind RCT of erythromycin in COPD, erythromycin (250 mgs twice per day) was compared with placebo in 109 COPD subjects (mean FEV_1 50% pred, 48% current smokers, no baseline exacerbation history) for 12 months [57]. Erythromycin significantly reduced exacerbation frequency (median 1 *versus* 2/ patient; RR 0.65) and time to exacerbation (271 *versus* 89 days). QoL was not reported.

The largest study of maintenance macrolides in COPD [49] randomised 1142 subjects (FEV_1 40% pred, 22% current smokers, 87% with exacerbation in the prior 12 months) to azithromycin (250 mg daily) or placebo for 12 months. Azithromycin significantly delayed time to first exacerbation (266 *versus* 174 days), reduced exacerbation frequency (mean 1.48

versus 1.83 per patient; RR 0.73, 95% CI 0.63–0.84) and improved QoL (mean change in St George's Respiratory Questionnaire score −2.8 *versus* −0.6). There was no effect on hospitalisations (323 in azithromycin group *versus* 329 in the placebo group).

In the most recent macrolide study, 92 COPD subjects with at least three exacerbations in the preceding year (FEV_1 44% pred, 32% current smokers, mean 4 exacerbations in the prior year; bronchiectasis excluded by CT scan) were randomised to azithromycin (500 mg three times per week) or placebo for 12 months [59]. Azithromycin significantly reduced the exacerbation rate (1.94 *versus* 3.22 per patient; adjusted RR 0.58, 95% CI 0.42–0.79) and delayed time to first exacerbation (130 *versus* 59 days), but not hospitalisations. There was no significant change in total St George's Respiratory Questionnaire score across the study, although scores for the symptom domain favoured azithromycin.

Other oral antibiotics (non-macrolide)

The only recent non-macrolide antibiotic prophylaxis study was a 48-week trial of pulsed moxifloxacin (400 mg given daily for 5 days every 8 weeks) in 1149 COPD patients with at least two exacerbations in the prior year (mean FEV_1 41% pred, 33% current smokers, mean 2.6 exacerbations in prior year) [50]. There was no significant effect of pulsed moxifloxacin upon exacerbations in the total trial population (number of patients with at least one exacerbation OR 0.87, 95% CI 0.69–1.09), although there were trends to a small reduction in exacerbation frequency (mean 0.88 *versus* 0.94 per patient; OR 0.81, 95% CI 0.65–1.01) and delay in time to first exacerbation (364 *versus* 336 days, $p=0.062$). There was no significant effect on QoL.

Summary of efficacy of prophylactic oral antibiotics for exacerbation prevention in COPD

There now exists compelling evidence supporting the efficacy of macrolides in exacerbation prevention in COPD, with consistency in the type and magnitude of this benefit across studies, at least for azithromycin and erythromycin. Furthermore, this benefit is consistent with that seen in other chronic inflammatory airway conditions in which bacterial infection (and sputum production) are features [60]: diffuse panbronchiolitis, CF and non-CF bronchiectasis [61]. Interestingly, clarithromycin has not been shown to exert a similar benefit in either COPD [56] or CF [62], although this may be a reflection of less evaluation of this agent rather than a lack of efficacy; nonetheless, clarithromycin use cannot currently be recommended on the basis of existing data.

Data supporting the use of non-macrolide antibiotics are weaker. Although studies before 1990 raise the possibility that typical antibacterial therapies might have a small impact on AECOPD, issues around patient selection, incomplete reporting of results, uncertainty around outcome definitions, and applicability to the current COPD population limit the ability to interpret the clinical relevance of these data now; the lack of uptake of this therapeutic paradigm in the 1970s and 1980s is informative in implying an ambivalence towards its perceived value. The only modern study of non-macrolide antibiotics [50] demonstrated no significant benefits although may have been underpowered or underdosed; either way, this was the largest COPD prophylactic antibiotic study to date, implying that any effect is likely to be small.

These data are also useful in considering the pathophysiology of AECOPD and particularly the role of bacterial infection, as it is unlikely that macrolides exercise their benefit predominantly through direct, traditional antibacterial effects. Macrolide antibiotics do not have conventional antimicrobial efficacy against *Pseudomonas aeruginosa* [63], and yet evidence suggests that it in both CF [64] and non-CF bronchiectasis [61, 65], they are most effective in the subgroup of patients infected with this organism. Furthermore, their activity against *Haemophilus influenzae* is modest (particularly for erythromycin) [66] and oropharyngeal streptococcal flora develop resistance rates of up to 90% within 3 days of commencing azithromycin [67], arguing against any direct anti-streptococcal effect from prolonged therapy. Conversely, moxifloxacin, an agent with activity against each of these pathogens, lacks significant effect on exacerbation reduction [50]. Finally, in non-CF bronchiectasis, the benefit of erythromycin is not related to effects upon respiratory microbiota composition [65].

The exact mechanisms by which macrolides achieve their clinical benefits remain unknown and may be both diverse and protean; a review of potential mechanisms is beyond the scope of the current chapter.

Risks of macrolide use in COPD

Adverse events

Neither the 2013 Cochrane review [48] nor the meta-analysis by Lee *et al.* [33] found any difference in the overall incidence of adverse effects with prophylactic antibiotics compared with placebo in COPD. However, there was an increased incidence of gastrointestinal adverse effects (OR 1.58, 95% CI 1.01–2.47) [48], mainly driven by a significant increase in these effects with moxifloxacin [50].

Macrolide antibiotics have generally been well tolerated in clinical studies, including in the COPD population. Gastrointestinal side-effects are the commonest adverse effect reported with these agents, particularly in azithromycin studies. Neither the RCT for erythromycin by Seemungal *et al.* [57] nor the RCT for azithromycin by Albert *et al.* [49] reported any increased incidence of gastrointestinal side-effects, although there was a significantly increased incidence of diarrhoea with azithromycin in the COLUMBUS study [59]. A meta-analysis of studies of macrolides in non-CF bronchiectasis found an increased incidence of gastrointestinal side-effects (RR 3.3, 95% CI 1.8–6.65) [68] although these were mild, self-limiting and did not lead to study withdrawal [69].

The primary concerns in relation to chronic macrolides are unfortunately less overt than simple adverse events and include cardiovascular risks, ototoxicity and antibiotic resistance.

Cardiovascular risk

Macrolide antibiotics can result in prolongation of the QT interval, in a dose-dependent manner [70], creating the potential for sudden cardiac death. Two US Medicaid observational cohort studies reported a small increased risk of cardiovascular death with the outpatient consumption of erythromycin [71] (5305 patient-years of use) or azithromycin [72] (347 795 prescriptions); both agents associated with approximately doubling of this risk over no antibiotic. However, a Danish population-based cohort study found no evidence of increased cardiac death with azithromycin use (>1 million prescriptions) in patients under 65 years of age [73]. The same investigators found a significantly increased risk of sudden cardiac death with outpatient use of clarithromycin (HR 1.78) but not roxithromycin [74].

The only prospective RCT to demonstrate increased cardiovascular risk with macrolides evaluated clarithromycin (500 mg daily for 2 weeks) or placebo given for 2 weeks to 4373 Danish patients with cardiac disease [75]. Clarithromycin was associated with significantly higher all-cause (RR 1.27, 95% CI 1.03–1.54) and cardiovascular mortality (RR 1.45, 95% CI 1.09–1.92). Strangely, this effect developed over 3 years of follow-up, with mortality risk accumulating over this period, rather than occurring within the period of clarithromycin administration, implying that QT prolongation was not the mechanism. In contrast, an RCT of azithromycin in 7747 patients with cardiac disease found no increase in mortality (and no divergence of curves) over 18 months of follow-up, with azithromycin in fact favoured (RR 0.92; p=0.42) [76]. There is no similar large RCT of erythromycin in patients with cardiac disease. A secondary analysis of two prospective UK datasets found that inpatient clarithromycin use was associated with an increased risk of cardiovascular events requiring hospitalisation in the following year among 1343 patients with AECOPD (RR 1.5, 95% CI 1.13–1.97) and 1631 patients with community acquired pneumonia (RR 1.68, 95% CI 1.18–2.38) [77]. Again, this risk developed over 12 months following clarithromycin consumption, rather than during the period of administration.

A US retrospective cohort study of patients over 65 years of age hospitalised for pneumonia found that azithromycin use (n=31 863) compared with non-use was associated with significantly lower 90 day mortality (OR 0.73, 95% CI 0.7–0.76) [78]. Azithromycin use was associated with an increased risk of myocardial infarction (OR 1.17, 95% CI 1.08–1.25) but not cardiac arrhythmias (OR 0.99, 95% CI 0.95–1.02) or any cardiac event; in contrast to the clarithromycin studies, Kaplan–Meier curves for cardiac events did not seem to diverge beyond about day 21. These findings corroborate other data suggesting that macrolide use reduces the risk of death in pneumonia [79].

In none of the clinical trials of erythromycin or azithromycin in any respiratory disease has there been any signal for increased cardiac adverse events reported and, in one study, reporting electrocardiogram monitoring, low-dose erythromycin over 12 months did not affect the QT interval [61]. In a recent meta-analysis of 12 RCT's (15 588 patients), azithromycin did not increase the risks of cardiovascular events (RR 1.0, 95% CI 0.92–1.09) and there was a trend to lower mortality (RR 0.88, 95% CI 0.75–1.02) [80].

The sum of evidence suggests that in patients with an appropriate clinical indication (hospitalised community-acquired pneumonia, CF, non-CF bronchiectasis or COPD with hospitalisation or frequent exacerbations), there are significant benefits of macrolides that outweigh any potential cardiovascular risks (except perhaps clarithromycin). It is important, however, to avoid their use in subjects who have QT prolongation or are being prescribed other medications that either prolong the QT interval or increase macrolide exposure. Even studies in patients with cardiac disease suggest no increased net risks with azithromycin [76, 80], although erythromycin or azithromycin should be considered cautiously in such patients [81]. The same cannot be said for clarithromycin, with concerning (although perplexing) data suggesting that it increases cardiovascular and mortality risks, but probably not *via* an arrhythmogenic mechanism [75, 77].

As argued recently [82], it is the use of macrolides outside clinically indicated conditions that poses risks of cardiovascular toxicity without significant benefits to mitigate these. Hence, outpatient prescription of macrolides for bronchitis or viral infections in the general population poses risks to consumers without evidence to suggest benefits to counterbalance these risks, and should be avoided; yet, staggeringly, approximately one-eighth of the US population received (outpatient) azithromycin in 2011 [82].

Ototoxicity

The evidence implicating ototoxicity as a result of macrolide therapy is limited to the study by Albert *et al.* [49], as no other study rigorously evaluated this outcome. Azithromycin resulted in significant hearing deterioration in the total population by 3 months (change in mean hearing threshold assessed by audiogram −0.7 *versus* 0 db; p=0.01), and 25% of azithromycin-treated *versus* 20% of placebo-treated subjects discontinued study drug due to hearing decrements (RR 1.39, 95% CI 1.05–1.85) [49]. The clinical implications of these findings, and the applicability to low-dose erythromycin (delivered at a much lower dose-equivalent in studies of chronic airways diseases) is unclear.

Microbiological consequences

Antimicrobial resistance

Antimicrobial resistance is an ancient phenomenon that far predates human antibiotic use, with resistance genes widespread in Late Pleistocene environmental samples [83]. Antibiotic resistance as a result of antibiotic use is inevitable [84]. Hence, this consequence should be expected and mitigated, as once "proof" arrives, the opportunity to prevent it has passed [85]. The use of macrolide antibiotics for antibiotic prophylaxis in COPD is no different in this regard. Why then, is there ongoing debate within the respiratory literature about whether or not the widespread use of prophylactic macrolides will influence antibiotic resistance?

A recent editorial explores some of the reasons that may account for this ongoing debate [86]. In brief, clinicians may fail to recognise that the risk does not primarily relate to the individual COPD patient taking the macrolide antibiotic but rather to the community around them; if sufficient COPD patients (a potentially enormous population [87]) take macrolide antibiotics, this will impact population-level antibiotic resistance to macrolides [60]. Secondly, identifying resistance in a limited selection of predefined, cultured respiratory pathogens will grossly underestimate resistance. The study by Albert *et al.* [49] illustrates just one of the reasons for this, showing reduced recovery of sputum pathogens in patients taking azithromycin (because azithromycin will suppress the growth of the pathogens), but substantially increased rates of macrolide resistance in the pathogens that were recovered. In order to accurately assess the impact of azithromycin upon rates of macrolide resistance requires a different method, such as measuring rates of proportional macrolide resistance within a bacterial community (whether pathogenic or not) in response to macrolides; measured in this way, average proportional macrolide resistance rates in oropharyngeal streptococci of nearly 90% are observed following only three doses of azithromycin in healthy volunteers [67], and 34% after 12 months of erythromycin therapy in bronchiectasis subjects [61]. All available data suggest that the more potent macrolides (particularly azithromycin) have a much greater effect upon induction of bacterial resistance than less potent agents like erythromycin. Figure 1 provides a startling illustration of the temporal relationship between azithromycin use and macrolide resistance rates in pneumococci in the USA; it should be remembered that erythromycin had been available and in use for some 40 years prior to this time.

The possibility that the continuous use of maintenance erythromycin might result in increasing macrolide resistance over time (eventually approaching 100%, as for azithromycin [67]) is countered by RCT data showing that resistance rates resulting from erythromycin therapy did not increase further after the first 28 days, even out to 12 months of continuous therapy [60, 61] (figure 2). These data suggest that the selection (and subsequent expansion)

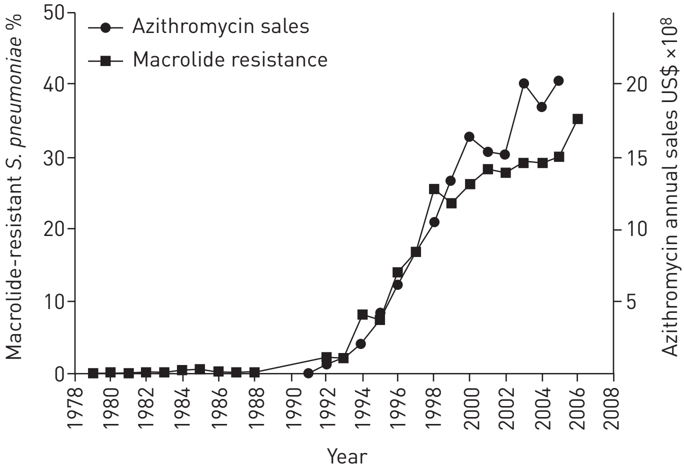

Figure 1. US rates of macrolide resistance in *Streptococcus pneumoniae* isolates and global Pfizer azithromycin annual sales data. Reproduced and modified from [60] with permission from the publisher.

of existing, resistant organisms from within the bacterial population [88, 89] was the primary mechanism of macrolide resistance development, rather than new, random mutations occurring under continued antibiotic exposure. Azithromycin therapy results in immediate, dramatic increases in macrolide resistance rates [67], a reflection of its much greater relative potency which results in near-extinction of sensitive organisms such that surviving organisms are almost entirely resistant variants [60]. Figure 3 illustrates this concept schematically, showing the immediate increases in macrolide resistance (which are also sustained after drug cessation due to its long half-life) resulting from 3 days of short-course azithromycin, while continuous, long-course erythromycin did not cause progressive increases in resistance rates in oropharyngeal flora over time.

Some researchers have questioned the *in vivo*, clinical relevance of *in vitro* macrolide resistance. However, animal studies clearly demonstrate the lack of clinical efficacy of

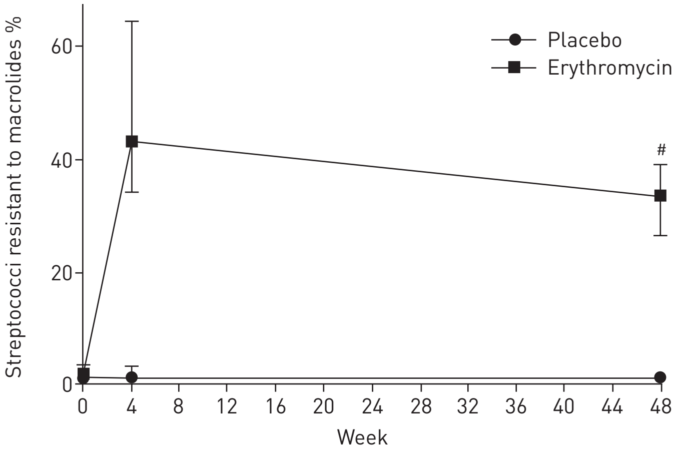

Figure 2. Changes in the proportion of macrolide-resistant oropharyngeal streptococci with erythromycin in non-CF bronchiectasis. Data are presented as median with error bars representing 95% CI. #: $p<0.0001$ compared with placebo for change from week 0 to 48. Reproduced and modified from [60] with permission from the publisher.

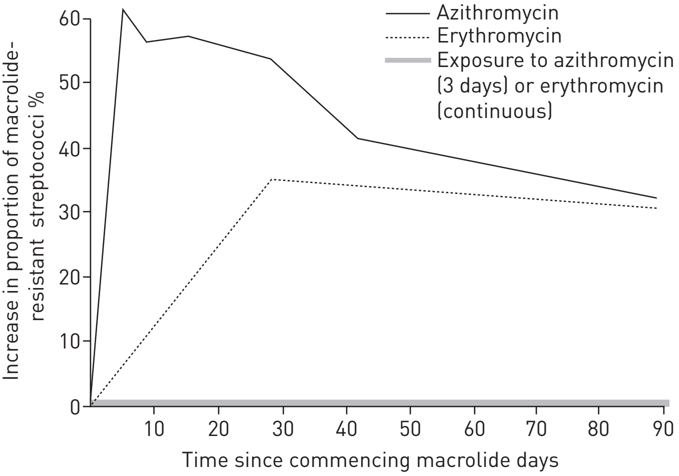

Figure 3. Schematic depiction of changes (from baseline levels) in the proportions of macrolide-resistant oropharyngeal streptococci over 3 months following either 3 days of azithromycin or continuous erythromycin. Data from [67] and [61].

macrolides against macrolide-resistant pneumococci in murine pneumonia models [90–92] and clinical studies have shown that *in vitro* macrolide resistance has *in vivo* consequences [93] including treatment failure [94], breakthrough bacteraemia [95] and even death from resistant *Streptococcus pneumoniae* [96]. Macrolide-resistance is also responsible for cases of acute rheumatic fever occurring during azithromycin therapy [60], and macrolide (and linked tetracycline) multiresistance is implicated in the expansion of group A streptococcal clones responsible for recurring outbreaks of scarlet fever occurring in China since 2011 [97]. Additionally: *erm* gene mutations (the commonest mechanism of macrolide resistance, responsible for 50–100% of macrolide resistant isolates in most studies) are commonly associated with co-resistance to teracyclines, lincosamides, streptogramins and chloramphenicol; data suggest that macrolide resistance potentiates penicillin- and multi-resistance in pneumococci [98, 99]; and macrolide consumption has been strongly associated with the development of community-acquired MRSA infection [100]. Finally, all of these prior data relate primarily to respiratory streptococci (for which alternative antimicrobial therapeutic options currently exist), hence the most alarming risks in fact relate to other organisms for which macrolides represent the sole option (or one of few), including *Legionella*, *Campylobacter*, *Bordatella pertussis* and multi-drug resistant *Salmonella* and *Shigella*. As a result of these concerns, macrolides are considered by the WHO to be “critically important antimicrobials” [101].

The development of antimicrobial resistance in individuals prescribed macrolides is inevitable, however the spread of this resistance to the broader community can be mitigated with two simple strategies: limiting the number of patients being prescribed these agents to those with more severe disease (the more restricted its application, the less likely it will influence population level resistance), and preferentially utilising erythromycin over the potent, broad-spectrum agent azithromycin [60].

Effects on respiratory microbiota composition

Next-generation sequencing data demonstrate that low-dose erythromycin therapy given to non-CF bronchiectasis patients significantly alters respiratory microbiota composition compared with placebo [65]. Subjects with *P. aeruginosa*-dominated airway infection demonstrated significant clinical benefits with erythromycin without significant change in respiratory microbiota composition. However, in subjects who did not have *P. aeruginosa*-dominated infection, there was no significant benefit of macrolide therapy upon exacerbation rates and there was a significant change in respiratory microbiota composition, representing the displacement of more macrolide-sensitive bacteria by organisms with greater macrolide tolerance, particularly *P. aeruginosa*. While the applicability of this to the COPD population is not clear, the potential for macrolide therapy to predispose patients to the development of overt *P. aeruginosa* airway infection over the long-term is of particular concern.

Pulmonary non-tuberculous mycobacterial infection

Azithromycin impairs intracellular killing of mycobacteria by blocking the ability of macrophages to lyse non-tuberculous mycobacteria (NTM) within phagosomes [102]. Consequent impaired clearance of NTM might explain observations that increasing rates of pulmonary NTM infection in CF (particularly *Mycobacterium abscessus*) may be associated with the use of long-term azithromycin [102]. Furthermore, widespread use of macrolides in chronic airways diseases increases the risks of promoting macrolide resistance in NTM, a situation associated with poor clinical outcomes [103] as macrolides are the most effective individual agents for treating this infection [104].

Should we use antibiotic prophylaxis in COPD? Balancing risks and benefits

Proven benefit of exacerbation reduction with antibiotic prophylaxis in the modern COPD patient is limited to macrolides. The widespread use of macrolides will influence bacterial resistance rates and may predispose subjects without respiratory *P. aeruginosa*-dominated airway infection to bacterial succession by this and other more antibiotic tolerant organisms, within respiratory bacterial communities.

A considered approach to the use of macrolides in COPD should consider the following points. While prevention of hospitalised exacerbations is likely to have substantial benefits to morbidity, mortality and healthcare resources, prevention of simple outpatient AECOPD may not [6, 7]. Secondly, the strongest predictor of future exacerbations and hospitalised exacerbations is a history of these same events [13]. Thirdly, current smokers have the greatest risks of accelerated lung function decline and data suggests that they are unlikely to benefit from maintenance macrolide therapy [105]. Finally, the risks of inducing population level antibiotic resistance will be determined primarily by both the resistance-inducing potential of the agent used and the proportion of people in a population who are exposed to it [60].

With these points in mind, the use of macrolide antibiotics should be limited to (currently non-smoking) subjects at risk of hospitalisation with COPD; that is, patients who have had previous hospitalisations for the same, or perhaps patients with a history of at least 3 exacerbations per year. Patients with COPD who are experiencing outpatient AECOPDs should be individually managed for those events as appropriate, without maintenance antibiotic use; if acute antibiotic therapy is indicated, a 5 day course of amoxicillin has far less ecological consequence than a year of daily azithromycin. Finally, the preferential use of erythromycin over azithromycin represents an ecologically responsible strategy.

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Inhaled medication: which device for which patient?

Mario Cazzola[1,2] and Paola Rogliani[1]

Case history: A 50-year-old man is seen in the clinic with newly diagnosed COPD. He is referred for smoking cessation and pulmonary rehabilitation but you feel he will also benefit from an inhaled long-acting bronchodilator. What factors would you consider in choosing the optimal medication for this man, with specific regard to the range of inhaler devices now available?

Chapter summary: Inhalation devices are a mainstay in the management of COPD. They include the pressurised metered-dose inhaler, dry powder inhaler, metered-dose inhaler with spacer, breath-actuated metered-dose inhaler, nebuliser and soft mist inhaler. Each type of device has its own advantages and disadvantages. The choice of device has to be tailored according to patient's needs, situation and preference. Certain factors, such as the age of the subject, the cognitive and psychomotor deficits occurring with the ageing process as well as a COPD-specific cognitive impairment, the availability of the drug formulation, the clinical setting as well as the disease being treated, the patient's ability to generate an adequate inspiratory flow, the capacity to handle the device appropriately and, importantly, its coordination with the inspiratory effort and the patient's preference for a device affect choice for the individual patient. Unfortunately, guidelines provide limited guidance regarding choice of devices, likely because of the lack of robust clinical data that can be translated into guideline recommendations.

Inhaled bronchodilators, which can be used individually or in combination with each other or ICSs, are still the cornerstone of the current management of COPD at all stages of the disease [1]. The use of inhaled therapy has a number of advantages over systemic (oral or intravenous) administration. It allows a smaller dose to be administered. Moreover, there is a faster onset of action and fewer systemic side effects.

Consequently, inhalation devices are a mainstay in the management of COPD. Correct use of an appropriate inhalation device enables medication to be effectively delivered directly to the lungs, thus maximising clinical efficacy while minimising potential systemic side effects [2]. Actually, inhalation (as opposed to systemic administration) allows drug dosages to be kept relatively low while remaining sufficiently effective because the drug is delivered directly to the airways, the site of action [3].

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Devices used in COPD

Many, perhaps too many, devices have been developed and each has specificities on how to prepare the dose and deliver the drug to the airways [4] (table 1). They include pressurised metered-dose inhaler (pMDI), for which, the drug is formulated in suspension or solution under pressure in a liquid propellant, which is subsequently released through an orifice as a spray upon device actuation; dry powder inhaler (DPI), for which drug is formulated as a powder that is fluidised and entrained as aerosol particles by the patient's own inspiratory effort; metered-dose inhaler (MDI) with spacer; breath-actuated MDI (baMDI); nebuliser, for which drug is formulated in aqueous solution or suspension and then atomised into droplets; and soft mist inhaler (SMI), which is propellant-free and delivers a metered dosage of medication as a fine mist.

Each type of device has its own advantages and disadvantages. For example, pMDIs require good coordination and a slow and deep inhalation, while DPIs require a turbulent flow to transform the metered powder formulation into disaggregated particles [5]. For DPIs, the inhalation flow must be maintained from the start of inhalation for a long period of time, so patients are required to breathe as deeply and forcefully as possible [6].

The wide range of inhaler devices that are available permits treatment to be tailored to patient's needs, situation, and preference [7], but at the same time it makes more difficult the correct choice of the right device for each specific patient. Unfortunately, until very recently no single manufacturer has produced a full range of medications required for managing COPD within the same type of inhaler. This implied that patients had to, and still must, learn to use two or more devices, each with different operating instructions, creating what has been labelled "device dementia" [8]. This is an important issue because we cannot ignore that patients develop strong preferences for specific types of inhalers, which can have an impact on adherence, particularly if they are switched to or must also use a different inhaler type [9]. The most effective treatment will not lead to better COPD outcomes if it is not used or if it is used incorrectly. In effect, each inhaler device has unique requirements for use that must be correctly performed by the patient for successful drug delivery.

Rationale for choosing one inhaler device over another

Patients with COPD represent a medically diverse population, with each patient having distinct characteristics, such as lung function, comorbidities, cognitive functions, hand strength and lifestyle [10]. While the choice of drug used for treatment is reasonably easy for the majority of COPD patients, the choice of delivery device is less clear, particularly in view of the ever growing, and at times confusing, number and types of devices that contain the same chemical entity.

In most cases, there is no evidence-based rationale for choosing one inhaler device over another, but certain factors affect choice for the individual patient [11] (table 2). One factor is the age of the subject. Another factor is the availability of the drug formulation, as not all drugs are available in each type of aerosol delivery device, which may limit choice when prescribing. The clinical setting (*e.g.* outpatient, emergency department, hospitalised inpatient, or intensive care setting) as well as the disease being treated (*e.g.* COPD *versus* asthma) influence the choice of aerosol device. Also the patient's ability to generate an adequate inspiratory flow, the capacity to handle the device appropriately and, importantly, its coordination with the inspiratory effort, considering that the decreased inspiratory and

Table 1. Advantages and disadvantages of different types of device in COPD

Device	Advantages	Disadvantages
DPI	Do not require coordination of inhalation with activation and do not require hand strength. Most patients can use a high-resistance DPI effectively, even during exacerbations.	Cognitive and psychomotor deficits occurring with the ageing process as well as a COPD-specific cognitive impairment are the principal elements restricting the correct use of the DPIs among the geriatric population. In the elderly, the ability to generate sufficiently high inspiratory flows through DPIs is compromised.
pMDI	Compact and portable, offer consistent dosing and rapid delivery, can be used independently and inconspicuously, and, sometimes, include a dose counter. For many COPD patients, it would be possible to achieve the slow inhalation flow required with a pMDI easily with training.	Patients with poor dexterity or weak grip strength, such as the elderly, may find it difficult to actuate a pMDI device. Failure of proper hand–breath coordination while using a pMDI will result in greatly reduced doses of drug reaching the lungs. A major problem with pMDI use is the so-called "cold Freon" effect.
MDI with spacer	Result in optimal lung deposition. Help by decreasing the oropharyngeal deposition of the medications and eliminating the "cold Freon" effect.	Aged patients may have difficulties assembling the pMDI with the spacer. The added size of a holding chamber or spacer defeats one of the primary advantages of the MDI, which is its compact size and portability and, to some extent, its immediate readiness for inhalation. The additional cost to the medical system is another major disadvantage.
baMDI	Requires an inhalation flow rate of only ~27 $L \cdot min^{-1}$ for actuation, which can be generated by patients with COPD. Elderly patients and those with arthritis have found the baMDI easier to use than the pMDI or DPI.	The available range of drug content can limit the use of the baMDI.
Nebulisers	Ability to aerosolise high doses of drugs that are not available with DPIs or pMDIs. Many nebulisers come with facemasks, meaning that aged patients and those with consciousness alterations can use them. Better clinical outcomes could be expected for patients who prefer to use nebulisers over other handheld inhalers as well as those who have difficulty using the pMDI or DPI.	There are no convincing data to show superiority of nebulisers for maintenance therapy in patients with COPD. Need for daily cleaning and longer time required for drug administration.
SMI	The relatively long generation time of the aerosol cloud facilitates coordination of inhalation and actuation. A considerably smaller dose of a combination bronchodilator, compared with delivery *via* the pMDI, results in the same level of efficacy and safety.	The metered volume of 15 µL limits the dose-delivery capacity of the marketed design to drugs with adequate solubility with respect to the required dose. The administration of tiotropium *via* Respimat may be avoided in patients with pre-existing cardiovascular comorbidities.

DPI: dry powder inhaler; MDI: metered dose inhaler; pMDI: pressurised MDI; baMDI: breath-actuated MDI; SMI: soft mist inhaler.

Table 2. Factors influencing selection of delivery device

The age of the subject
The availability of the drug formulation
The clinical setting as well as the disease being treated
The patient's ability to generate an adequate inspiratory flow
The capacity to handle the device appropriately and, importantly, its coordination with the inspiratory effort
The patient's preference for a device

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expiratory flow rates and decreased inspiratory capacity of the COPD patient may also pose important problems in the choice. Moreover, the patient's preference for a device should not be disregarded. The prescribing clinician must select the most appropriate drug–device combination for the patient carefully, taking into account all these elements [3].

Dry powder inhaler

The typical DPI is a passive device (*i.e.* relying on patient inspiratory effort). The majority of patients with COPD are advanced at the time of diagnosis. They are middle-aged or older and some of the more severely affected patients are elderly. Physical and cognitive changes, the presence of arthritis or joint pain and also neuromuscular conditions like Parkinson's disease or complications after stroke contribute to the difficulties some elderly patients have with handheld inhalers [12, 13]. Effective use of a DPI requires that each dose must be primed and loaded. Therefore, cognitive and psychomotor deficits occurring with the ageing process as well as a COPD-specific cognitive impairment are the principal elements restricting the correct use of the DPIs among the geriatric population [14]. Nonetheless, COPD patients appear to make fewer device-handling mistakes when using a DPI than when using a pMDI [15]. In fact, advantages of DPIs are that they do not require coordination of inhalation with activation and do not require hand strength.

Patients with COPD suffer from severe expiratory airflow limitation typically accompanied by decreased inspiratory capacity, hyperinflation and respiratory muscles that work at a mechanical disadvantage. All of these factors combine to reduce inspiratory flow rate [16]. In effect, several COPD patients, especially those with moderate and severe obstruction, may have problems achieving the minimum inhalation rate required through a DPI [17]. A low force of inspiration may result in insufficient drug deposition in the lung and excessive deposition in the patient's mouth or pharynx [18, 19]. This may lead to mouth dryness and adversely affect medication adherence. Swallowing the dose that remains in the oropharynx can contribute to systemic adverse events. In patients with COPD, age and sex are more important determinants of inspiratory flow through DPIs than the degree of expiratory airway obstruction [17]; although in elderly patients, the ability to generate sufficient inspiratory flow across a DPI is compromised, irrespective of the presence of COPD [20].

Fortunately, most COPD patients are able to generate inspiratory flows that are sufficient for optimal drug delivery to the lower airways [17]. Moreover, it is beginning to become more widely understood that there is not unique inspiratory flow rate nor pressure drop for optimal use of DPIs [21]. Clinical experience shows that most patients can use a high-resistance DPI effectively, even during exacerbations. DPIs fall into two main classes, according to whether their constant fine particle fraction (the mass fraction of the dose emitted in the size <5 µm range) output is dependent on, or independent of, the user's inspiratory flow rate [21]. For DPIs with a constant fine particle fraction at all flow rates, less of the delivered dose reaches the central and peripheral lung when the flow rate increases, risking under-dosing of the required medication. In contrast, flow rate-dependent inhalers increase their fine particle fraction output at higher flow rates, which compensates for the greater impaction on the upper airways as flow rate increases [21].

The ideal device to be used by a COPD patient has a universal design, is independent of patient inspiratory force and can deliver a consistent and reproducible dose into the lungs with patient compliance [22]. Based on their design, DPI devices may currently be classified into three broad categories: first-generation, single-dose DPIs; second-generation, multiple-dose DPIs; and third-generation DPIs, also known as "active" or power-assisted DPIs.

First-generation DPIs are breath-activated, single-dose devices in which a capsule of powder is perforated in the device with needles fixed to pressure buttons; with these inhalers, drug delivery is affected by particle size and de-agglomeration of drug carrier agglomerates or mixtures delivered by the patient's inspiratory flow [22].

Second-generation multi-unit devices were developed as more convenient alternatives to single-unit devices although they also have their limitations. A complaint against multiple-dose DPIs is a lack of feedback to the user to show that the correct dose has been delivered and to continuously show how many doses remain. However, multi-unit DPI devices, *i.e.* devices that dispense individual doses which are pre-metered into blisters, disks, dimples, tubes and strips by the manufacturer and also include a dose counter, which have been developed recently, are associated with high patient satisfaction and seem to be easier to use and preferred by patients than single-dose DPIs [23, 24]. This is an important issue because development of an inhaler that is regarded as easy and intuitive to use may have positive implications for adherence to therapy in COPD.

It is noteworthy that the newer-generation DPIs are "active", power-assisted devices, which incorporate battery-driven impellers and vibrating piezo-electric crystals, to disperse drug from the formulation, thus reducing the need for the patient to generate a high inspiratory flow rate, an advantage particularly for patients with impaired lung function [25]. Due to the presence of an energy source, active DPI devices enable respiratory force-independent dosing precision and reproducible aerosol production. These devices are obviously more sophisticated than passive DPIs, and, unfortunately, are likely to be relatively expensive devices for COPD therapy [22]. Nevertheless, we believe that they may be the most useful devices for delivering drugs in patients with severe respiratory failure.

Pressurised metered-dose inhaler

The primary advantages of a pMDI are that it is compact and portable, offers consistent dosing and rapid delivery, can be used independently and inconspicuously, and sometimes includes a dose counter. For many COPD patients, it would be possible to achieve the slow inhalation flow required with a pMDI easily with training [26].

However, the advantages of pMDIs are limited by the need for a specific breathing technique that involves coordination between inspiration and actuation, slow and steady inspiration, and a breath hold [27]. Patients with poor dexterity or weak grip strength, such as the elderly, may find it difficult to actuate a pMDI device. Indeed, a report by CONNELLY [28] (studying 19 elderly patients with an average age of 78 years) suggested that ∼10% were unable to trigger a conventional pMDI device. Failure of proper hand–breath coordination while using a pMDI will result in greatly reduced doses of drug reaching the lungs. However, even with the correct inhaler technique, only a comparably small fraction of the dose delivered by suspension pMDIs actually reaches the lungs [29].

The second major problem with pMDI use is the so-called "cold Freon" effect, in which the cold blast of propellants causes patients either to stop inhaling or to inhale *via* the nose; this is probably less marked with hydrofluoroalkane formulations [30].

In effect, compared with old chlorofluorocarbon-driven pMDIs, many hydrofluoroalkane-driven pMDIs deliver an aerosol plume with a lower impact force and a higher temperature [31]. These properties partially overcome the cold Freon effect [22]. Moreover, new developments in drug formulation have allowed for the development of new pMDIs that produce aerosols containing extra-fine particles [32]. Extra-fine particle pMDIs demonstrate equivalent efficacy to other preparations but with a reduced equivalent dose of corticosteroid or bronchodilator [32]. These newer formulations have been reported to be less dependent upon inhaler technique than other MDIs due to longer duration of aerosol emission and lung deposition being affected less by inspiratory flow and coordination [32]. Smaller particle size, lower plume velocity and less temperature drop may decrease upper airway impaction and increase airway deposition of particles, particularly to the smaller airways, compared with the same drug administered from a chlorofluorocarbon-driven pMDI [22]. This is very important for patients with COPD whose lungs need to be deflated. Inhaled extra-fine particles targeting the peripheral lung are a particularly attractive strategy to pharmacologically deflate patients with COPD, as increased small airway resistance is a key mechanism of air trapping in these patients [33].

MDI with spacer

The obvious limitation of need for coordination can easily be overcome with the use of a holding chamber called a spacer device (preferably a large volume one) [3], which would result in optimal lung deposition and additionally helps by decreasing the oropharyngeal deposition of the medications and eliminating the cold Freon effect [34]. Importantly, valved holding chambers allow the patients to breathe tidally from a reservoir of drug, thus reducing the need of coordination between inhaler actuation and inhalation [35]. When added to the pMDIs, they slow down the emitted aerosol, reduce aerosol loss when inhalation is delayed, and may increase the pulmonary deposition from around 10% using a pMDI to 20% or more [36].

However, the walls of the spacers retain some of the drug, making it impossible to know how much is actually delivered into the airways. Moreover, aged patients may have difficulties assembling the pMDI with the spacer [37], and, in any case, the added size of a holding chamber or spacer defeats one of the primary advantages of the MDI, which is its compact size and portability, and, to some extent, its immediate readiness for inhalation [2]. Moreover, the additional cost to the medical system is another major disadvantage [2].

Breath-actuated MDI

The baMDI produces softer and more efficiently delivered spray and represents a user-friendly alternative to traditional pMDIs. They have been designed to sense the patient's inhalation, and to actuate the pMDI automatically as the patient inhales [38]. Patients who have coordination problems with MDIs but otherwise have an appropriate speed of inhalation may benefit from being prescribed a baMDI [39]. The baMDI requires an inhalation flow rate of only approximately 27 $\text{L}\cdot\text{min}^{-1}$ for actuation that can be generated by patients with COPD [40]. Moreover, elderly patients and those with arthritis have found the baMDI easier to use than the pMDI or DPI [40]. Unfortunately, the available range of drug content can limit the use of baMDIs [41].

Nebuliser

Nebulisers convert solutions and suspensions into small droplets. Solutions are comprised of drug dissolved in a carrier liquid, whereas suspensions are comprised of solid drug particles suspended in the carrier liquid. An advantage of using nebulisers includes their ability to aerosolise high doses of drugs that are not available with DPIs or pMDIs [42]. In addition, many nebulisers come with facemasks, meaning that aged patients and those with consciousness alterations can use them [42]. However, a facemask should ideally be avoided if a nebulised steroid is administered (to avoid steroid administration to the facial skin and eyes) and also if anticholinergic agents are to be administered to patients with glaucoma [43].

Various nebulisers are available, each with different properties. There are two types of nebulisers, jet and ultrasonic, which differ in the force used to generate the aerosol from the respective liquid. Therefore, the choice of nebuliser device should be considered carefully. The selection of the most appropriate nebuliser relies largely on considering drug and patient factors. Advanced devices, such as breath-activated nebulisers, would be required when precise drug delivery and reduced drug wastage are essential, whereas conventional jet nebulisers can be suitable for drugs with a wide therapeutic index and when ease of use and economy are required [44].

The majority of the patients consider pMDIs to be more convenient than nebulisers and nebulisers to be more effective than pMDIs for inhaled drug delivery [44]. In some instances, preferences for a nebuliser may reflect psychological issues, the fact that the patient is usually obliged to rest during a nebuliser treatment, or they may have problems with correct use of a pMDI, DPI or SMI [29]. Generally these patients tend to be older, more debilitated and more severely obstructed. They may find nebuliser delivery of their medications to be more effective since an optimal dose is delivered by normal (tidal) breathing, regardless of disease state [45]. Moreover, nebulisers are indicated for patients with COPD who are undergoing severe exacerbations, especially those with alterations of consciousness [42].

Although there are no convincing data to show superiority of nebulisers for maintenance therapy in patients with COPD, better clinical outcomes could be expected for patients who prefer to use nebulisers over other handheld inhalers as well as those who have difficulty using pMDIs or DPIs [46]. As such, it has been recommend nebulised delivery of drugs for COPD in the following situations [46]: 1) elderly patients, particularly male patients over 65 years of age; 2) patients with severe disease and frequent exacerbations; 3) patients who have physical and/or cognitive limitations; 4) for inhalation drug delivery during exacerbations of COPD, especially when higher than routine drug doses are needed; 5) when monetary concerns favour nebulised therapy over other inhalers; and 6) patients who prefer nebulised therapy over other inhalers.

In any case, it is noteworthy that an Italian study showed that patients using nebulisers were significantly more likely to perform critical errors in using an inhaler than those using inhalers only [47]. This observation emphasises that there is a subgroup of patients who will not be able to use inhalers and who might benefit from nebuliser therapy.

The disadvantages cited for nebulisers in the literature are not ones of patient use but rather the need for daily cleaning and longer time required for drug administration [48].

Soft mist inhaler

The SMI is a new-generation inhaler that functions by forcing a metered dose of drug solution through a unique and precisely engineered nozzle (the Uniblock), producing two fine jets of liquid that converge at a pre-set angle [49]. The collision of these two jets generates the soft mist. The soft mist contains a high fine particle fraction of approximately 65–80%. This is higher than aerosol clouds from conventional portable inhaler devices, such as pMDIs and DPIs. In addition, the relatively long generation time of the aerosol cloud (~1.5 s) facilitates coordination of inhalation and actuation, a major problem with pMDIs [50]. These characteristics should result in improved lung and reduced oropharyngeal deposition [50]. Clinical studies support the higher drug deposition in the lung compared with aerosols produced by DPIs or pMDIs. In fact, a formulation containing only one-half or one-quarter of the dose of a combination of bronchodilators delivered by a pMDI results in the same level of efficacy and safety [51]. However, the metered volume of 15 μL limits the dose-delivery capacity of the marketed design to drugs with adequate solubility with respect to the required dose. The limitations of the dose-delivery capacity could be overcome by increasing the volume or number of puffs administered, but this would have to be balanced against the risk of reduced patient compliance [51].

COPD patients generally prefer SMI (Respimat; Boehringer Ingelheim; Ingelheim am Rhein, Germany) to pMDIs and to at least one common DPI (Handihaler; Boehringer Ingelheim) [52]. However, although the massive TIOSPIR (Tiotropium Safety and Performance in Respimat) trial showed that tiotropium when administered *via* Respimat 5 μg is not less safe than Handihaler 18 μg [53], it has been suggested that the administration of tiotropium *via* Respimat may be avoided in patients with pre-existing cardiovascular comorbidities [54].

Conclusion

For optimal treatment of COPD, consideration of patient characteristics when recommending and prescribing an aerosol delivery device can help to minimise device-use errors [46]. The patient's age, cognitive status, visual acuity, manual dexterity, manual strength and ability to coordinate actuation of the inhaler with inhalation of the aerosol released may be as important as disease severity in determining the appropriate approach to delivery of medication. For many patients, using a nebuliser alone or in addition to a pMDI or DPI provides an easy-to-use and cost-effective therapy [46]. Obviously, administration of effective therapies *via* a device that is simple to use and accepted by patients may help to improve treatment outcomes in patients with COPD.

Patient satisfaction with and preference for a specific inhaler device are extremely important and have attracted increasing attention in recent years, because of the potential impact that patients' experiences with their inhalers might have on adherence to therapy and hence long-term outcome [55].

Dekhuijzen *et al.* [56] have suggested that an optimal match between patient and device may be achieved by applying a simple four-model question ("Who": consider COPD disease characteristics; "What": consider the type of drug to use; "Where": targeting the medication; and "How": matching patient, molecule, dose and device) approach. This means that a better matching between patient and device could be accomplished if the physician is aware of: 1) the patient characteristics (disease, severity, fluctuation in airflow obstruction, *etc.*); 2) what class of medication is indicated; 3) where in the lung the medication should be delivered; and, 4) how this can be best achieved by a given device in this specific patient.

Obviously, this is an empirical approach, but guidelines provide limited guidance regarding choice of devices, likely because of the lack of robust clinical data that can be translated into guideline recommendations [57].

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Chapter 16

The importance of physical activity

Daniel Langer[1,2], Heleen Demeyer[1,2], Thierry Troosters[1,2] and
Rik Gosselink[1,2]

Case history: A 69-year-old man with COPD ($\mathrm{FEV_1}$ 59% predicted, 6MWD 85% pred) visits the outpatient clinic after 1 week of wearing an activity monitor. The device shows that the patient currently has a physical activity level of $4500\ \text{steps}\cdot\text{day}^{-1}$. Is this patient sufficiently active? Would you coach him towards a higher physical activity level?

Chapter summary: The promotion of a physically active lifestyle is recommended for all patients with COPD, based on a large evidence base of the health benefits of being physically active. The available physical activity recommendations differ considerably. It has been demonstrated that these differences have a significant impact on the classification of patients with COPD into categories of sufficient and insufficient physical activity. Functional capacity and functional reserve become increasingly limited with progressing disease severity. This makes it difficult for many patients to achieve the recommended time in physical activity of at least moderate intensity. Reducing sedentary time might be a relevant and more realistic treatment goal in these patients. Objective measures are available to measure physical activity and their characteristics make these tools suitable for use in clinical practice. Treatment approaches to modify physical activity have gained popularity in recent years. Self-monitoring of daily activities and goal setting with feedback from a pedometer are common elements in these interventions, which have the potential to improve health in patients with COPD.

Physical inactivity is thought to play a crucial role in the development of COPD comorbidities (*e.g.* osteoporosis, anxiety and depression, diabetes, cancer, muscle weakness, and cardiovascular disease) [1]. Promotion of a physically active lifestyle has been recommended as part of the non-pharmacological treatment of all patients with COPD, mainly based on the large evidence base of benefits of being physically active that exists in the general population [2, 3]. Prospective epidemiological studies have demonstrated that the risk of all-cause mortality is lower in physically active adults than in their inactive counterparts [4], and that a mid-life increase in physical activity reduces the risk of all-cause mortality [5].

The field of research regarding physical activity in patients with COPD has increased exponentially in the last decade. This growing interest is based on data showing the differences in physical activity behaviour between patients with COPD and healthy,

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age-matched controls [6]. In a systematic review that summarised 11 studies investigating physical activity in patients with COPD, a significant decrease in the duration and intensity of physical activity was observed, with intensity being less affected than duration (75% and 57%, respectively, of values observed in healthy controls) [7]. These results were confirmed in a recent, large cohort study [8]. In the study, patients with COPD presented with a reduction in time spent in low or moderately intense activities in comparison with their healthy counterparts [8]. The physical activity level of patients has been shown to drop dramatically during and after a hospitalisation for an acute exacerbation and is lower in patients with frequent exacerbations [9]. Pitta *et al.* [9] observed markedly lower physical activity values 1 month after hospital discharge when compared with physical activity levels in stable patients with COPD. In comparison with other chronic diseases, such as diabetes and rheumatoid arthritis, the prevalence of inactive patients is significantly higher in COPD [10].

The decrease in physical activity is already present early in the disease [11], and worsens with progressing disease severity [12]. Even (ex-)smokers unaware of their airflow limitation show reductions in physical activity when compared with (ex-)smokers without airflow limitation [13]. The potential mechanisms explaining the presence of (early) physical inactivity and worsening throughout the course of the disease are illustrated in figure 1. Abnormalities in pulmonary function and gas exchange (leading to higher ventilatory requirements during exercise), as well as skeletal muscle dysfunction are already present to a variable degree in early disease stages and can contribute to the perception of increased exertional dyspnoea and leg fatigue [11, 15, 16]. These symptoms make exercise an unpleasant experience and patients probably adapt to this by decreasing their physical activity, most likely beginning with nonessential leisure activities followed by activities of daily living. This results in an inactive lifestyle, which is likely to aggravate exercise limitation [12, 15]. Deconditioning and muscle weakness are physiological consequences of inactivity that can also be observed in healthy subjects within 2 weeks of reduced physical activity [17]. These data suggest that reductions in physical activity will lead to deconditioning, worsening of dyspnoea and a further reduction in physical activity levels [12, 15]. This brings patients into a vicious cycle of inactivity that is difficult to reverse [15].

In addition to reductions in physical activity, impaired exercise capacity is also common in patients with COPD [18]. Although functional capacity is correlated with physical activity,

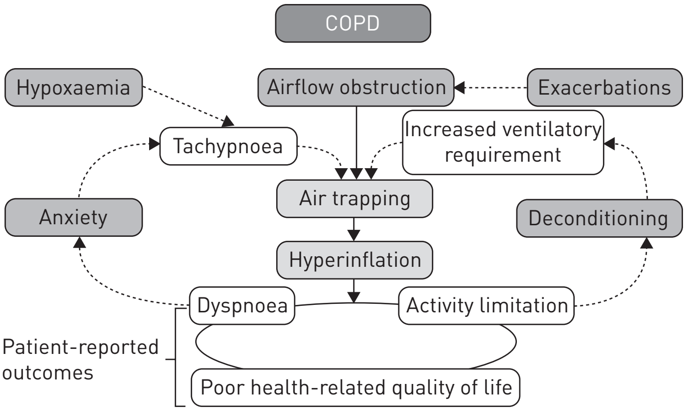

Figure 1. Vicious cycle of symptoms and inactivity. Reproduced and modified from [14] with permission from the publisher.

both present different entities and it is important to make the distinction between both outcomes, as explained in a theoretical framework by Leidy [19] and shown in figure 2.

Functional capacity is defined as the maximum potential to perform activities that people might engage in during the normal course of their lives to meet basic needs, fulfil usual roles, and maintain health and well-being [20]. Functional performance (physical activity) is defined as all activities people actually do in the normal course of their lives (including activities for personal bodily needs like dressing and eating, hobbies, visiting friends, and psychological and spiritual activities). In the remainder of this chapter, the term physical activity will be used as a synonym for functional performance. Functional reserve is the difference between capacity and performance. The closer to functional capacity one is performing activities, the more exertion is required to complete these activities. Increasing one's capacity implies that the performance can be reached with less exertion than before. Engagement in daily physical activity is partially the outcome of an individual choice, especially in subjects with preserved functional capacity. In individuals with more limited functional capacity, this freedom of choice may be restricted, as illustrated in figure 3 [6, 19].

In summary, a distinction should be made between two different concepts: functional capacity, indicating what a patient is capable of doing; and physical activity (functional performance), reflecting what a patient is actually doing.

Definitions

Physical activity (functional performance) has been defined as: "any bodily movement produced by skeletal muscles resulting in energy expenditure" [21]. Exercise is defined as a subset of physical activity that is planned, structured, repetitive and has the aim of improving or maintaining physical fitness [21]. Physical activity also comprises other

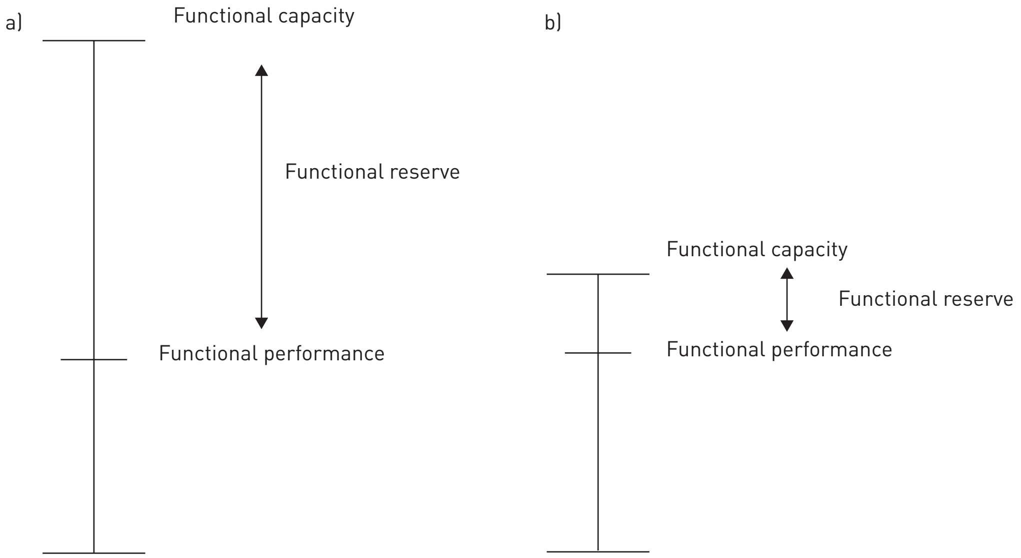

Figure 2. Schematic representation of the relationships between functional capacity, functional performance and functional reserve in a) healthy subjects and b) patients with severe COPD. Reproduced and modified from [19] with permission from the publisher.

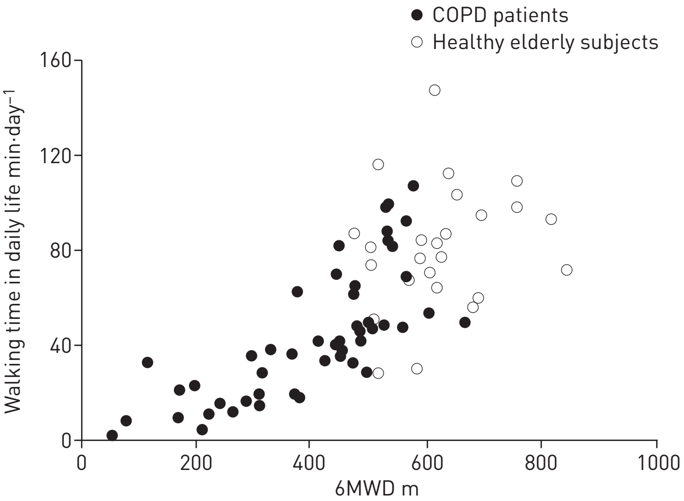

Figure 3. Plot of 6MWD and walking time in daily life assessed during 12 h·day^{-1} in patients with COPD (n=50) and healthy elderly subjects (n=25). It is apparent that in patients with COPD, who have a more limited functional capacity (6MWD), physical activity expressed as walking time in daily life (performance) and 6MWD (capacity) are more closely related (R^2=0.56; p<0.0001) than in healthy elderly subjects whose capacity is better preserved. In the group with larger functional reserve, the scatter widens and the relationship between the two variables becomes less strong (R^2=0.07; p=0.3). Reproduced and modified from [6] with permission from the publisher.

components besides exercise, such as domestic and occupational tasks, and basic, everyday tasks required for self-care and independent living.

Physical activity is often classified in activities of light, moderate, vigorous or very vigorous intensity, based on the energy expenditure of the performed activity. Often, classifications are based on the metabolic equivalent of the task (MET). One MET represents resting energy expenditure (upright sitting), equal to 3.5 mL oxygen consumption·kg^{-1}·min^{-1}. Energy expenditure of an activity will be expressed relative to the resting oxygen consumption. For example, a task performed with an intensity of 3 MET requires three times the resting energy expenditure. An outcome frequently used in the literature is the time in physical activity of at least moderate intensity (MPA), comprising time in moderate, vigorous and very vigorous intensity, because this variable has been included in physical activity recommendations.

Sedentary behaviour is defined as any waking behaviour characterised by an energy expenditure of <1.5 MET in a sitting or reclining posture [22]. Sedentary behaviour occurs during the waking day, which means sleep is not included in the definition. Common sedentary behaviours are watching television, driving a car and reading.

Recommendations

Physical inactivity is usually defined as a level of physical activity that is below an optimal threshold [23]. This is based on strong evidence relating insufficient levels of physical activity to negative health outcomes in the general population [24]. Individuals are considered sufficiently active if they accumulate 30 min of at least MPA on ⩾5 days every week [25–27]. These 30 min per day should be performed over and above light intense activities performed in the course of daily living, and can be accumulated in bouts of

$\geqslant$10 min with maximal 2 min of interruption within one bout [25–28]. The definition of MPA varies, however, between different guidelines. It has been further demonstrated that differences in the definition of MPA have a significant impact on the classification of patients with COPD as sufficiently or insufficiently physically active [29, 30]. The most commonly used definitions are summarised in table 1.

Functional capacity and functional reserve might become very limited in the elderly or in patients with chronic diseases like COPD. This will make it difficult for these subjects to achieve recommendations based on MPA as defined by absolute MET cut-off values. The American College of Sports Medicine therefore recommends that for these populations, MPA cut-points relative to the capacity of an individual (*e.g.* 40% oxygen uptake (V'_{O_2}) reserve or 50% maximal V'_{O_2}) could be used to classify activities as moderately active [25, 27]. Although this approach makes intuitive sense, its validity in terms of resulting in health benefits has, to the best of our knowledge, not yet been supported by data.

The differences between absolute and relative recommendations for patients with different degrees of expiratory flow limitation are illustrated in figure 4. Reductions of time spent in MPA according to an absolute 3 MET cut-off follow the same pattern as reductions in functional capacity with progressing disease severity. Patients become severely inactive and only engage in a very limited amount of MPA as defined by an absolute 3 MET cut-off. This is probably caused by the fact that in these patients >3 MET activities have to be performed at a high percentage of their capacity (small functional reserve). This also becomes apparent when the amount of MPA is reported based on a definition using an intensity cut-off relative to capacity (in this case 50% of V'_{O_2} reserve). As functional capacity becomes smaller, these patients perform large parts of their day at >50% of their functional reserve. The observed relationship between higher levels of fatigue and increasing limitations in expiratory flow and functional capacity might also be related to these observations [32]. This is likely to have implications on the ability of these severely limited patients to increase their levels of physical activity, even though they are very sedentary.

While most guidelines provide recommendations based on duration and frequency of performing MPA (defined as either absolute or relative to capacity), there are also step-based recommendations available [25, 31]. Step-based recommendations are based on a total volume of activity (minimal number of steps) that should be accumulated on a daily basis. The absolute threshold for older adults ($\geqslant$50 years of age) to be sufficiently active has recently been estimated to be around 7000 steps (table 1). A "step-defined sedentary lifestyle index" of 5000 steps$\cdot$day^{-1} has also been suggested [33]. The proposed volume of 7000 steps$\cdot$day^{-1} is based on an estimated background of 5000 steps$\cdot$day^{-1} (which may actually be

Table 1. Physical activity recommendations for health based on absolute, relative or step-based definitions

Recommendation [ref.]	Frequency	Intensity	Duration	Volume
Absolute [25, 26]	$\geqslant$5 days$\cdot$week^{-1}	$\geqslant$3 MET	$\geqslant$30 min$\cdot$day^{-1}	
Relative [25, 27]	$\geqslant$5 days$\cdot$week^{-1}	$\geqslant$50% V'_{O_2max} or $\geqslant$40% V'_{O_2} reserve	$\geqslant$30 min$\cdot$day^{-1}	
Step-based [31]				$\geqslant$7000 steps$\cdot$day^{-1}

MET: metabolic equivalent of the task; V'_{O_2max}: maximal oxygen uptake; V'_{O_2}: oxygen uptake.

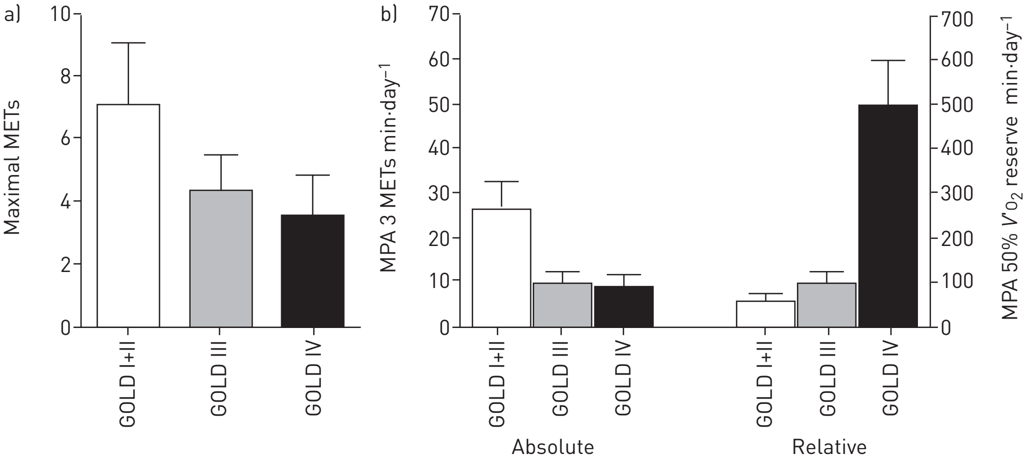

Figure 4. Functional capacity and differences between absolute and relative classifications of moderate physical activity (MPA) in patients with different degrees of expiratory flow limitation. a) The functional capacity of patients in three different Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages. It is apparent that capacity is on average more limited in patients with more severe disease. b) Duration of time spent in MPA (*i.e.* functional performance) based on either absolute or relative definitions. MET: metabolic equivalent of the task; V'_{O_2}: oxygen uptake. Data from [30].

an overestimation in older adults and/or special populations (figure 5)), and an estimated increase to 8000 steps·day^{-1} on 5 out of 7 week days [31]. It has been proposed that this increase in daily step count (3000 additional steps at a cadence of 100 steps·min^{-1} on 5 out of 7 week days) should be comparable to adding 30 min of MPA·day^{-1} on 5 out of 7 week days on top of background activities as recommended in absolute MET-based guidelines (table 1) [25, 26]. In a similar manner to absolute MET-based recommendations, elderly subjects, or those living with a disability and/or chronic illness might have difficulty achieving these recommendations. These individuals frequently display lower levels of background daily activity (figure 5), and might not be able to attain step cadences of 100 steps·min^{-1}.

Step-based recommendations relative to the capacity of elderly or frail individuals are not currently available. Most pedometer-based activity interventions base their goals on increases relative to baseline background activity levels (discussed further later). Normative steps per day values for elderly subjects have recently been published [34]. These normative values will facilitate the comparison of measured steps with expected background activity levels in different age groups. Normal average step values do not represent desirable values but rather give an indication of activity levels that are currently being observed in different age groups. While the evidence for step-based guidelines is even less extensive than for MET-based recommendations, this outcome has the advantage that it can be assessed with less advanced measurement equipment (discussed further later).

Physical activity assessment

Self-report

Participation in physical activity can be assessed with questionnaires. However, the practicality of these instruments for individual use in clinical practice is limited. Recall bias, the tendency

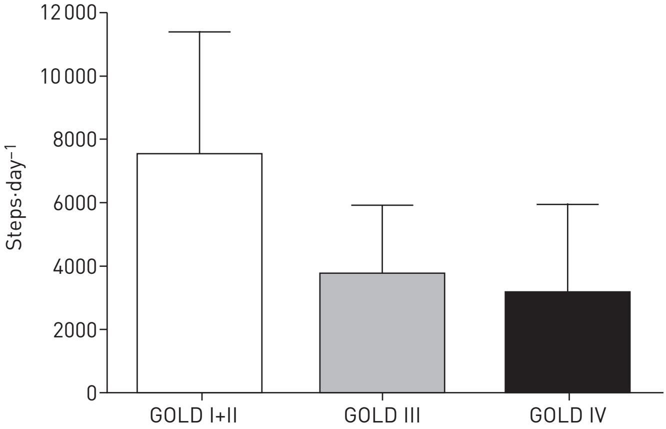

Figure 5. Volume of physical activity presented as mean steps per day in patients with different degrees of airflow limitation. GOLD: Global Initiative for Chronic Obstructive Lung Disease. Data from [30].

to provide socially desirable information (especially of low-intensity and unplanned "background" activities), and the lack of responsiveness when detecting small changes in physical activity after interventions, are well known limitations to the measurement of physical activity with questionnaires [23, 35–38]. Existing physical activity recall assessments have been estimated to capture no more than 50% of the variance in free-living physical activity levels, and often much less [39]. However, because of the efficiency, utility and low cost of this approach, self-reports of physical activity are often used in large epidemiological studies [23, 36]. In a recent review, it was found that although a total of 15 questionnaires aiming to measure physical activity to some extent had been developed for patients with COPD, none of them was actually based on a conceptual framework, ensuring that the tool would measure concepts relevant to patients [40]. This gap is currently being filled by a project that aims to develop and validate a patient reported outcome measuring physical activity from a patient perspective (www.proactivecopd.com), based on a conceptual framework [41].

Objective measures

Objective measures of physical activity do not rely on information provided by the patient, but instead register biomechanical and/or physiological consequences of performing physical activity [42]. We will focus on accelerometers and pedometers as their small size, low participant burden and relatively low cost make these objective tools suitable for use in clinical practice.

A pedometer is an electronic or electromechanical device worn on the waist or hip that counts each step a person takes by detecting the acceleration of the body's centre of mass during the gait cycle [42]. Steps are registered when the acceleration signal exceeds a critical threshold. The primary limitation of pedometers is that they do not register the intensity of the detected movement. Another limitation of some pedometers might be an underestimation of steps during walking at slow speeds [43–45]. This may limit the usefulness of some devices in patients with severe activity limitation. It might be that some devices perform better than others but each pedometer will need specific validation at walking speeds adopted by patients.

Accelerometry-based motion sensors have become one of the most commonly used methods for assessing physical activity [23, 42]. These devices are commonly worn on the hip, wrist or back and typically sample the acceleration of the body along three axes (tri-axial accelerometers). The acceleration signal is then filtered, rectified and integrated to provide an estimate of physical activity duration and intensity. Accelerometers are sometimes combined with other sensors that register physiological signals, such as heart rate or skin temperature, and are then referred to as combined-activity monitors [23]. These additional signals might improve the estimates of activity intensity, especially during activities that are known to be difficult to assess with pedometers and accelerometers. Activities such as cycling, lifting or carrying objects, and the increased energy cost associated with walking an incline or walking up stairs fall into this category [42].

The validity of objective measures for assessing physical activity in patients with COPD has been the subject of many investigations in recent years [23, 46]. Two studies recently validated six widely used devices against gold standard measurements [47, 48]. The DynaPort MiniMod (McRoberts BV, the Hague, the Netherlands), the Actigraph GT3X (Actigraph, Pensacola, FL, USA) and the SenseWear Armband (BodyMedia, Inc., Pittsburgh, PA, USA) (all employing tri-axial accelerometers) appeared to be sufficiently valid and responsive for use in COPD.

The number of assessment days and hours of use per day are also important factors that may influence the reliability of the physical activity assessment [49, 50]. For cross-sectional analyses, 2–3 days is sufficient for reliable measurement of physical activity in Global Initiative of Chronic Obstructive Lung Disease (GOLD) stage IV patients, whereas up to 5 days of measurement might be required in patients with GOLD stage I [49]. Four measurement days (excluding weekends) were shown to be sufficient to detect changes in physical activity following PR in moderate-to-severe COPD [50].

Health benefits

Healthy population

In the healthy population, the benefits of being physically active and the harm of being inactive are well documented [3, 25]. Benefits include a reduction in cardiovascular disease, type 2 diabetes, cancer, dementia, the risk of falling and all-cause mortality [25]. Being physically active preserves bone mass and enhances well-being, quality of life and cognitive function [25]. Interestingly, the protective effects of physical activity on (cardiovascular) morbidity and mortality are independent of the benefits related to physical fitness [51].

Mounting evidence suggests that reducing time in sedentary behaviour may also have important health benefits and, more importantly, these benefits seem to be independent of MPA as defined by absolute cut-offs [52]. In this context, it is important to realise that a person can spend sufficient recommended time in MPA but can still engage in sedentary behaviour for the largest part of the day. An example of such behaviour is seen in elite cyclists, who combine intensive non-weight-bearing exercise with periods of sedentary time (rest, sleep). These subjects were shown to be at high risk of developing osteoporosis [53]. This concept of low-level background activity has been named the "active couch potato" [52]. Besides the total duration of sedentary time, breaks in this behaviour (*e.g.* breaking a sitting behaviour by standing) were shown to have a positive effect on important biomarkers of chronic disease [54]. Accordingly, a more comprehensive view of inactivity has recently been proposed that takes into account the health impacts of physical activity across a spectrum of sedentary to vigorous activity (figure 6) [52].

COPD patients

In patients with COPD, physical activity has been consistently associated with a reduced risk of hospital admission and mortality [55]. The level of physical activity has been shown to be the most important independent predictor of all-cause mortality in this population. In a large trial of >1400 patients hospitalised for AECOPD, it was observed that physical activity levels at baseline together with dyspnoea and hospital location were significant modifiable predictors of the hospital length of stay [56]. This suggests a direct association between physical activity and the use of health services and related costs. In patients discharged from hospital, those who were less active (objectively measured using an accelerometer) during the week following discharge were more likely to be readmitted within 30 days, independent of the exacerbation history in the preceding year; this was known to be the most important predictor of hospitalisation risk [57]. These results were confirmed in a large trial (>4500 patients) based on self-reported physical activity levels [58].

Several population-based studies investigating the relationship between physical activity and lung function decline demonstrated an inverse relationship [59–63]. This beneficial effect of regular activity seems to be present in active smokers, prior to COPD development, which can be seen as a slower decline in lung function in the more active subjects [64].

Reduced physical activity is associated with greater disease severity (worse lung function) [64, 65], higher levels of dyspnoea [64, 65], lower exercise capacity [66–69] and lower health-related quality of life [65, 70–72], but these conclusions are based on low- to very low-quality research from mostly cross-sectional studies [55]. How being physically active affects balance and bone mineral density is inconsistent in the literature [55]. From recent data collected in a population-based cohort of preclinical patients with COPD ((ex-) smokers unaware of their airflow limitation), it was concluded that inactivity and smoking,

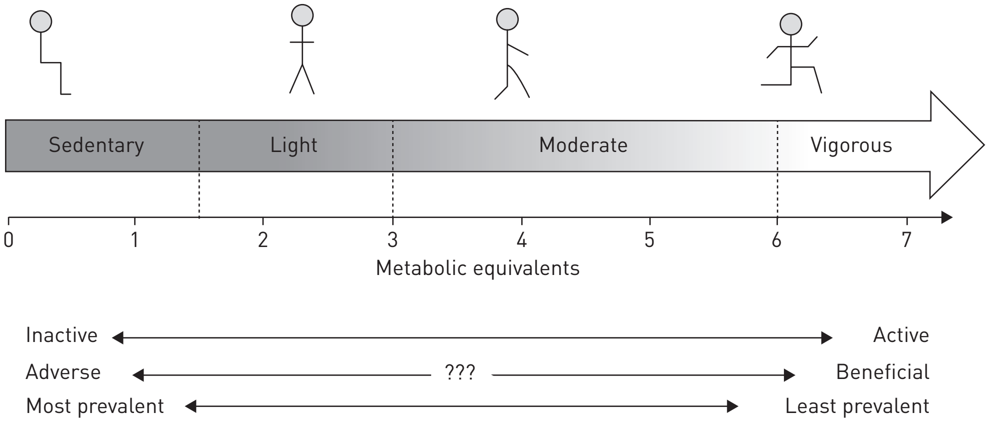

Figure 6. Comprehensive view of health impacts across the full spectrum of physical activity intensity. Reproduced and modified from [52] with permission from the publisher.

rather than the disease COPD as such, were the main risk factors for developing comorbid conditions [73].

Besides the health benefits of being physically active, the direct effects of changing physical activity behaviour are important to notice here, although literature on this is scarce. In a recent study, it was observed that patients with COPD who decreased their physical activity levels had an increased mortality risk, but a protective effect of an increase in physical activity on mortality could not be found [74]. Esteban *et al.* [75] showed that patients who changed to a higher level of physical activity or maintained a moderate or high level of physical activity over 2 years of follow-up, showed a decreased rate of exacerbations requiring hospitalisation in the next 3 years. Both studies were based on self-reported physical activity levels.

The consequences of increased sedentary behaviour in patients with COPD, which has already been shown by Pitta *et al.* [6] to be present as an increased sitting and lying time, independent of the MPA level, have not yet been investigated. It may be that decreasing sedentary time is a more relevant and realistic goal for patients with severe COPD, in whom functional reserve is too small to expect an increase in MPA (based on absolute MET cut-offs) (figure 4b). In healthy adults there is a strong negative correlation between sedentary time and time in light-intensity physical activity; individuals who have a positive light–sedentary balance (more time spent in light-intensity physical activity than sedentary time) show cardiometabolic benefits [52]. Although no direct evidence is available, these data suggest that an increase in light-intensity activities, a decrease in total sedentary time and breaking this sedentary behaviour might be relevant treatment goals for patients.

Treatment strategies to improve physical activity

In the following section, several treatment options will be discussed that could be used to increase participation in physical activity in patients with COPD. The focus will be both on treatments that mainly aim at increasing functional capacity (*e.g.* supervised exercise training during PR (figure 2)) and on treatments that aim to specifically modify physical activity behaviour (functional performance (figure 2)).

Pulmonary rehabilitation

Several studies have investigated the effects of PR upon short- and long-term changes in physical activity, and have found on average only minor changes in physical activity, despite significant improvements in functional capacity [43, 76–85]. From analyses performed in three recent studies, it might even be concluded that the effects of rehabilitation on participation in daily physical activity seem to be largely unrelated to improvements in functional capacity [78, 84, 85]. These results are in line with findings from cardiac and orthopaedic rehabilitation programmes. In these populations, it has also been shown that a high percentage of patients failed to maintain an active lifestyle after acutely increasing their exposure to structured and planned physical activity (*i.e.* supervised exercise training) during a rehabilitation programme [86]. Activities that are more easily integrated into daily life, such as Nordic walking, might be a good alternative or might be used as an adjunct to traditional supervised exercise regimens in selected patients [87]. Widespread acknowledgment of this physical activity-maintenance problem has led to the recognition of daily physical activity as a complex behaviour that probably needs to be targeted with specific interventions. Whether all patients will respond to such interventions is questionable. It is plausible that a minimum amount of functional capacity is needed before physical activity becomes a realistic target for treatment. In addition to functional capacity and symptoms experienced during activity, behavioural and environmental factors have also been shown to be related to participation in daily physical activity in patients with COPD [55].

Modification of patient behaviour

Key components that increase the effectiveness of behavioural interventions targeting physical activity in populations other than COPD have already been summarised in several meta-analyses and international guidelines [85, 88–93]. Greater effectiveness of interventions to change physical activity behaviour has been shown to be causally linked to mobilising social support and the use of well-described/well-established behaviour-change techniques [89]. These established techniques include self-monitoring, stimulus control, problem solving, relapse prevention management, goal setting, self-reinforcement and developing action plans [88, 89, 91]. Larger improvements were associated (in correlational analyses and non-randomised comparisons) with using a cluster of self-regulatory techniques (goal-setting, self-monitoring, providing feedback on performance, goal review) and providing a higher contact time or frequency of contacts [89]. It has also been suggested that we should assess not only the actual behaviour (*i.e.* participation in daily physical activity) but also the readiness/motivation to change in order to apply interventions according to stages of readiness [89]. Motivational interviewing techniques have been recommended as a collaborative communication approach that seems to have a greater effect than the traditional directive communication between the healthcare provider and the patient [89]. These findings are consistent with recent guidelines from the American Heart Association (AHA) on the prevention of heart disease, which recommend the use of motivational interviewing as well as goal-setting, self-monitoring and a high contact frequency in interventions to promote regular physical activity [94]. In a systematic review in 2012, which investigated the effectiveness of activity monitor-based counselling programmes in patients with chronic diseases, evidence of a beneficial effect in patients with diabetes mellitus type 2 and a lack of data in patients with heart failure and COPD was reported [95].

Wearable monitors that provide feedback to users have been used in numerous physical activity research projects in different sedentary adult populations. A meta-analysis of these studies dating from 2007 showed that home-based pedometer walking programmes are successful in getting inactive people to walk ~2000 steps (30%) more per day over their baseline levels [96]. Only one of the studies included in this meta-analysis investigated the effects of lifestyle physical activity counselling with pedometer feedback in patients with COPD [76]. DE BLOK *et al.* [76] found a 1000-step difference in increasing daily activity by adding a physical activity counselling programme to a 9-week PR programme, in comparison with a control group. More recently, the effects of pedometer-based programmes in patients with COPD have been investigated in more detail and increases in daily physical activity ranging 600–3000 steps have been reported in comparison with control groups [97–102]. Two studies reported a pedometer-based intervention, during which patients were coached by telephone [100, 101]. KOVELIS *et al.* [103] found large and statistically significant effects on daily activity (+3000 daily steps) of a 4-week pedometer feedback intervention in inactive smokers. MOY *et al.* [104] reported a significant increase of 1300 steps·day^{-1} that was induced by a 3-month website-based counselling programme with pedometer feedback in patients with COPD.

A different approach was taken by Pleguezuelos *et al.* [105], who tried to manipulate environmental factors by implementing urban walking circuits. Implementation of walking circuits in patients with COPD resulted in an increase in physical activity of 30 min per day in comparison to a control group after 9 months of follow-up, as assessed by self-report [105]. Creating a healthy and safe environment for physical activities might be a crucial prerequisite for individuals to become more active. This is also promoted by an initiative of the World Health Organization (WHO), called Healthy Cities [106].

In summary, strategies to modify physical activity behaviour are gaining popularity in the COPD population and these interventions seem to have the potential to increase participation in physical activity. Overall, however, the evidence base is limited and studies involve small samples. Often, programme content has not been clearly defined, but self-monitoring of daily activities and goal setting based on relative increases in baseline background activity with pedometer feedback, were common elements in most of these studies. Wearable devices created by several large technology companies are gaining popularity and are marketed to promote health behaviour change. It is important to stress that while these devices have the potential to facilitate behaviour change, the success of interventions will depend on engagement strategies that are built around these tools rather than on the technology itself [107].

Conclusion

Promotion of a physically active lifestyle has been recommended as part of the non-pharmacological treatment of all patients with COPD, based on a significant body of evidence on the benefits of being physically active that exists both in the general population and in patients. A distinction should be made between functional capacity, indicating what a patient is capable of doing, and actual functional performance (*i.e.* physical activity), reflecting what a patient is actually doing in daily life. Available physical activity recommendations differ from each other regarding the definition of MPA, and it has been demonstrated that these differences have a significant impact on the classification of patients with COPD into sufficiently or insufficiently physically active groups. Functional capacity and functional reserve become increasingly limited with progressing disease severity. This will make it difficult for many patients to achieve recommendations based on time in physical activity of at least moderate intensity, as defined by absolute MET cut-off values. Objective measures of physical activity (accelerometers and pedometers) are available and their characteristics make these objective tools suitable for use in clinical practice. Although no direct evidence is available, it might be that decreasing sedentary time is a relevant and realistic goal for patients with (severe) COPD. Strategies to modify physical activity behaviour have gained popularity in recent years. Self-monitoring of daily activities and goal setting based on relative increases in baseline background activity with feedback of a pedometer were common elements in most of the available studies. These interventions have the potential to increase participation in physical activity and improve health in patients with COPD.

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Chapter 17

How to assess the benefits of pulmonary rehabilitation

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Case history: Mr X is a 65-year-old patient with severe COPD (FEV_1 35% predicted) referred to PR 2 weeks after discharge from an acute exacerbation. He has now completed 12 weeks of PR, consisting of exercise training three times per week. In addition to training, Mr X received dietary support (high protein/calorie advice), prescription of a rollator walking aid, occupational therapy (energy conservation techniques) and consultations with a respiratory nurse to develop self-management skills aiming to enhance appropriate actions upon subsequent exacerbations. Mr X improved his 6MWD by 52 m and his FEV_1 by 150 mL compared with the assessment upon entry to PR. Is this a comprehensive outcome assessment? How should the benefits of PR best be assessed?

Chapter summary: This chapter summarises the methods for assessing the effectiveness of comprehensive PR programmes, with consideration given to the different perspectives of patients, therapists, referrers and funding bodies. The assessment and treatment of PR attendees should be specific and patient centred, to maximise the attainment of individual goals across a diverse range of clinically important outcomes. The main domains of assessment include evaluation of exercise capacity, peripheral muscle strength, health-related quality of life, symptoms and physical activity levels. Assessment of additional, specific factors (*e.g.* nutrition, anxiety/depression, self-efficacy) may be indicated for selected patients if problems are identified upon admission to PR. Finally, consideration is given to some of the important issues affecting PR in order to improve the standardisation and comparability of future programmes.

Pulmonary rehabilitation is an evidence-based treatment for patients suffering from COPD, even in the period following an acute exacerbation [1]. Significant benefits are usually observed in terms of exercise tolerance, quality of life, symptoms [2, 3], psychological morbidity [4] and utilisation of healthcare resources [5]. The latter is particularly true for fragile patients who experience acute exacerbations, as the likelihood of experiencing an exacerbation increases with previous episodes [6]. Positive outcomes are obtained from PR despite a very wide scatter of programme designs, duration, content and patient eligibility. Similarly, there is a wide range of outcome measures to assess patients

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that enter rehabilitation and capture benefits of the rehabilitation process [7]. There is a need for standardisation of PR outcomes in order to provide feedback on progress to patients and their family, enable cross comparison (bench marking) of programmes, provide transparent data on progress to referrers, and satisfy the needs of regulators and funding bodies to show continuing intervention effectiveness. Figure 1 summarises individual responses to a 3-month outpatient PR programme in 480 patients with COPD at the authors' centre in Leuven (Belgium). The high individual variability in responses underpins the necessity for detailed, patient-centred assessment in order to accurately determine the effects of PR.

This chapter provides a comprehensive overview of the methods and outcome measures to consider in order to capture the benefits of rehabilitation in areas that are 1) relevant to understand the mechanisms of physiological improvement in order to fine-tune the programme in individual patients, 2) relevant to patients, 3) relevant to funding bodies, and

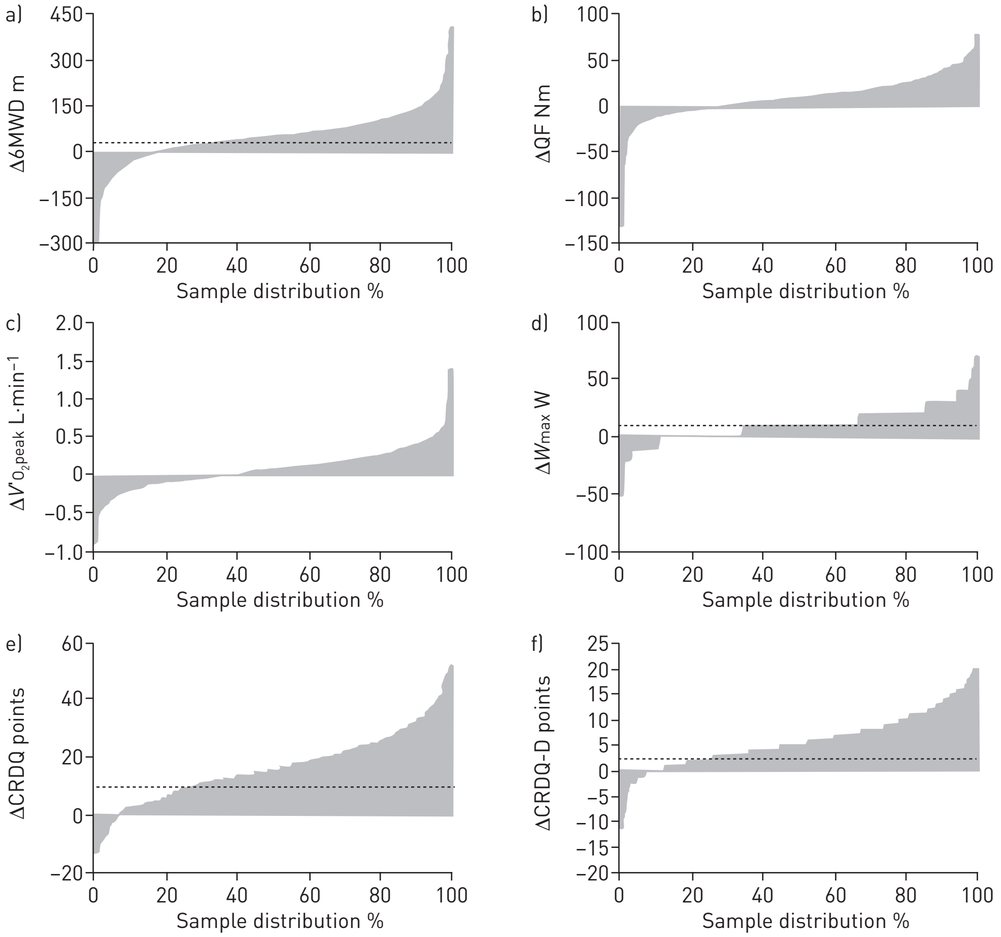

Figure 1. Effectiveness of a 3-month PR programme in patients with COPD. Δ: change from baseline to 3 months; QF: quadriceps muscle force; $V'_{O_2\text{peak}}$: maximal oxygen uptake from cardiopulmonary exercise test; W_{max}: maximal workload from cardiopulmonary exercise test; CRDQ: Chronic Respiratory Disease Questionnaire (total score); CRDQ-D: dyspnoea domain of CRDQ. Dotted lines represent minimal clinically important difference.

4) relevant to implement quality control of the programme, benchmarking and prepare for programme audits. We will closely follow the guidance of the statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [1]. Prior to entering PR, a comprehensive assessment of patients should be undertaken in order to identify the most appropriate type of programme, modalities of training and other interventions. This review will focus on the end-points used to capture the benefits of PR programmes, in a broad sense. While brief summaries of common clinical outcomes will be described, including information regarding their possible expected average magnitudes of change (*e.g.* minimal clinically important differences (MCIDs) for specific tests), it is important that each individual's responses to PR are evaluated relative to their personal circumstances. Therefore, determining the benefits of PR at the individual level may not always be simplified down to an "exact" science. This review will provide a global overview of many of the key aspects that clinicians should consider in the comprehensive assessment of PR effectiveness.

Evaluation of the physiological benefits of exercise training

Exercise training is the cornerstone of PR. When conducted according to current guidelines [1] for sufficient duration and at appropriate intensity, significant physiological benefits can be expected in the majority of patients. Up to one third of patients, however, may not benefit as desired (figure 1) [8, 9]. Understanding individual responses during a training programme can enable early identification of patients likely to derive suboptimal benefit and facilitate modifications to the training stimulus, a strategy proposed to enhance PR training effects [10].

Evaluation of functional exercise performance

The effects of the exercise training component of PR are best captured by direct assessment of exercise performance (capacity or tolerance) and the factors that constitute their limitations (*e.g.* muscle, lung and cardiovascular function). Several assessments have been proposed for such purposes, ranging from complex cardiopulmonary exercise testing to field tests of walking performance. Despite this large range, there is no single "best" test for use in PR programmes. Table 1 summarises the properties of the most commonly reported exercise tests in the COPD PR literature.

Maximal exercise tests offer significant opportunity to determine patients' true maximal exercise capacity and identify important physiological factors that may limit exercise tolerance. The largest magnitude of response (sensitivity) to exercise training, however, is undoubtedly detectable *via* an endurance test conducted at a constant work rate on a bicycle, treadmill or in a walking corridor. This occurs as patients approach the limits of the ventilatory system more slowly, allowing insight into exercise performance beyond that of rapid ventilatory limitation. Such tests may therefore play a more important role in the evaluation of the success of such interventions, compared with maximal tests. Other tests, such as the 6MWT, are responsive, and have the advantage of a well-described MCID [18]. Measures of gas exchange, ventilation and heart rate allow judgement of the physiological mechanisms of improvement in individual patients. Evaluation of the effectiveness of exercise training programmes, however, has most commonly been determined *via* simple field tests. Although these are unquestionably effort-dependent tests, they are easier to implement in the clinical routine. In recent years, more comprehensive "functional" tests have been described in the context of PR. Examples include the Glittre test [19], the 4-m gait speed test [20] (performed either at comfortable or maximal walking speed), and the

Table 1. Commonly used tests for the evaluation of functional exercise performance in PR

Test name	Available outcomes	Sensitivity to PR	Minimal important difference
Incremental exercise test	Peak work rate	+	5–10 W [11, 12]
	Peak V'_{O_2}	+/–	
	Ventilation (V'_E) at iso-load	+	
	Symptoms at iso-load	+	
Incremental shuttle walk test	Distance/time	++	47.5 m (~5 shuttles) [13]
	Symptoms at iso-time	+/–	
Constant work rate test	Time to exhaustion	+++	100–200 s or 33% improvement [14–16]
	Iso-time measures	++	
	Exercise metabolic kinetics#	+	
Endurance shuttle walk test	Time s	++	186 s for PR [17]
	Distance m	++	
6MWT	6MWD	++	25–30 m [11, 18]
	6-min walk work¶	+/–	

V'_{O_2}: oxygen uptake; V'_E: minute ventilation. +, ++ and +++: positive responses; +/–: uncertain. #: outcomes only available if metabolic monitoring equipment *in situ*; ¶: 6MWD×weight.

timed-up-and-go test [21]. As these tests are not extensively used in a rehabilitation context, their potential additional value to existing PR outcomes is not yet clear.

Evaluation of skeletal muscle function

Exercise training aims to enhance peripheral muscle function. Patients with skeletal muscle weakness and fatigable peripheral muscles seem the best candidates for exercise training [8, 9]. Assessment of skeletal muscle strength should therefore be assessed prior to starting PR; however, this is not yet routinely performed in all PR settings [7]. Evaluation of muscle force may also yield important prognostic information due to the known significance of specific muscle groups (*e.g.* quadriceps, handgrip) as predictors of adverse health outcomes [22, 23]. Diverse methods to assess muscle force exist and can be applied in the clinical setting. A recent statement from the ATS/ERS has outlined some of these assessments, describing when and where they can be applied [24].

Available techniques for assessing muscle strength include the one-repetition maximum (1RM) method (*i.e.* the maximal weight a subject can lift over the full range of motion), handheld dynamometry, isokinetic dynamometry and non-volitional assessments using magnetic nerve stimulation. As muscle weakness/wasting in patients with COPD is typically a “global” body phenomenon (*i.e.* unilateral differences rarely observed), evaluation of the unilateral body limb is adequate unless significant comorbidities are present (*e.g.* significant knee osteoarthritis affecting one limb). The isometric maximal volitional strength assessment is a reliable and reproducible test that is relatively simple to implement in clinical practice (*e.g. via* strain gauge mounted to a chair) [24]. In COPD, isometric measurements of muscle strength demonstrate good responsiveness to exercise training (mean improvement ~25%, range 12–53%) [25]. The addition of specific resistance training to an endurance training programme significantly enhances peripheral muscle strength [26, 27].

Skeletal muscle endurance can also be measured; however, there is less consensus regarding the best method for conducting this test. Testing is more time consuming to perform and less clinical value is demonstrated. Typically, the number of repetitions at a given weight is measured and tests prove highly responsive to change.

Improvements in skeletal muscle strength and endurance are the result of adaptations in the neuromuscular system. In order to answer specific research questions related to skeletal muscle responses to exercise training, other tests have been used, such as non-volitional tests of skeletal muscle strength and skeletal muscle fatigability. Such tests are rarely used in clinical practice due primarily to their complexity, high equipment costs and time-consuming procedures [28]. Similarly, invasive skeletal muscle biopsy tests are essential to answer mechanistic research questions, but are not routinely investigated.

Recently, several functional tests of skeletal muscle function have found their way to the field of PR. Such tests typically involve motor functions and rely to a large extent (but not solely) on skeletal muscle performance. An example of such a test is the five-repetition sit-to-stand (5STS) test [29], in which patients are asked to rise from and sit down on a chair without using their arms, five times. While such tests have documented responsiveness to PR (MCID of 1.7 s for the 5STS [29]), it is important to note that functional tests commonly involve interaction of multiple body systems and may not be ideal substitutes for more traditional methods of evaluating single systems (*e.g.* muscle force). The 5STS test, for example, is only weakly associated with quadriceps maximal voluntary contraction ($r=-0.33$, but statistically significant) and is influenced by postural balance and proprioception [30]. Other tests that have been recently implemented in PR include those used to evaluate functional balance [31]. These may help to identify patients at risk of falling, but have not yet been thoroughly investigated in a PR context to establish responsiveness (*i.e.* reduced risk of falling). Such research is essential before these tests are more widely recommended for use in contemporary PR outcome assessment.

Evaluation of physical activity

PR should aim to enhance physical activity. Physical activity should therefore be assessed, objectively, prior to and following rehabilitation. Reliable instruments exist to capture physical activity in patients with respiratory disease, but in general the effects of PR on the amount of physical activity are modest [32] unless specific interventions are introduced to enhance physical activity. Despite the fact that enhanced physical activity is an important outcome of rehabilitation, it is not routinely assessed in many rehabilitation programmes. With advancing technology and reduced complexity of the assessment techniques, it is expected that physical activity assessment will become more commonplace over the next decades. A comprehensive overview of physical activity testing and associated outcomes is provided in another chapter of this *Monograph* [33].

Evaluation of symptoms

Symptom improvement is crucial to patients [34]. In COPD, high-intensity training reduces the ventilatory needs for given tasks, improves muscle function and improves breathing patterns [35] and respiratory muscle function. In addition, the neural processing of dyspnoea may be altered, leading to less perception of dyspnoea even when the physiological context is identical [36]. The implementation of targeted strategies to better manage limiting symptoms such as dyspnoea, including prescription of rollators during walking and breathing/relaxation strategies, offers additional potential for symptom relief on top of these physiological and neural adaptations. It is therefore unsurprising that symptoms during exercise or during daily life tasks are also reduced.

Symptoms of dyspnoea and leg fatigue are commonly assessed during formal exercise challenges. It is important that such symptoms are measured in a standardised manner for given exercise tasks, as factors such as assessment timing may significantly influence interpretation of test performance. For example, symptom scores obtained at the end of a 6MWT upon PR completion may not accurately reflect the true improvement from PR admission, as walking performance will be affected not only by improved symptoms, but also improved (increased) walking speed. Evaluation of symptoms at iso-time (an identical time-point before and after rehabilitation, *e.g.* 4 min into a test) during an incremental or fixed-pace (matched to baseline level) endurance exercise task may be a better alternative.

The effect of symptoms on everyday activities is commonly evaluated *via* questionnaires. The Chronic Respiratory Disease Questionnaire (CRDQ), for example, evaluates dyspnoea intensity during five activities that patients identify as the most important in their daily life. The range of instruments to evaluate symptoms is large and diverse (table 2) and outcome choice should be determined according to the symptom construct (*e.g.* the sensation/descriptor, severity, impact on daily function) and appropriate time period relevant to the PR programme.

Evaluation of other patient-reported outcomes

Patient-reported outcomes (PROs) capture improvements of PR from a patient-centred perspective in domains relevant to patients. PROs have the advantage of capturing the patient's experience directly and without interaction of a health professional [43]. They therefore describe the perceived benefits of rehabilitation more directly than (for example) exercise tests or tests of skeletal muscle strength. PROs have been developed in several domains relevant to patients in the context of PR, yet, interestingly, very few PROs have been developed in accordance with the rigorous methodologies required by regulatory agencies [43, 44]. Nevertheless, many PROs are well established in PR, have clear guidance as to what constitutes a clinically significant effect and are relatively easy to use. PROs can capture concepts like health status (health-related quality of life), daily life experience, functional status (or performance) and symptoms such as fatigue or dyspnoea (table 3).

PR is associated with clinically relevant improvements in psychological well-being (*e.g.* depression or anxiety) [52, 53]. This is particularly true for patients who report problems at the start of the programme [54]. In clinical practice, follow-up assessment of these factors is unlikely to be necessary in all PR attendees; rather, it could be reasonably confined to those who exhibit needs before or during PR.

Evaluation of knowledge, self-management and self-efficacy

Patients who attend PR typically have learning needs that can be appropriately addressed within the interdisciplinary PR environment. The best methods for providing education during PR are not clear; however, formal didactic group-based education sessions appear to

Table 2. Commonly used instruments to evaluate symptoms in PR programmes

Domain	Instrument name	Clinical application		Recall period	Minimal important difference
		During exercise	During daily life		
Dyspnoea	Modified Borg dyspnoea scale	✓	×	Immediate	1 point [37]
	Visual Analogue Scale	✓	×	Immediate	10–20 mm [37]
	Baseline/Transitional Dyspnoea Index	×	✓	Short–medium term (days–weeks)	1 unit [38]
	Dyspnoea-12	×	✓	Short–medium term (weeks)	
	UCSD Shortness Of Breath Questionnaire	×	✓	Short–medium term	5 units [39]
	Modified MRC dyspnoea scale	×	✓	Medium–long term (weeks+)	1 point
	CRDQ-D	×	✓	Medium–long term (weeks+)	0.5 point per item [40]
	St George's Respiratory Questionnaire	×	✓	Medium–long term (weeks+)	4 points [40]
	Multidimensional Dyspnoea Profile	×	✓	Medium–long term (weeks+)	
Fatigue	CRDQ-F	×	✓	Medium–long-term (weeks+)	2 points [40]
	Borg rating of perceived exertion scale	✓	×	Immediate	1 point [37]
	COPD and Asthma Fatigue Scale	×	✓	Short–medium term (1+ weeks)	
	PFSDQ-M (fatigue subscale)	×	✓	Medium–long term (weeks)	3–6 points [41]
	FACIT-fatigue	×	✓	Short–medium term (1+ weeks)	3–4 units [42]
	Multidimensional Fatigue Inventory	×	✓	Short–medium term (weeks)	

UCSD: University of California, San Diego; MRC: Medical Research Council; CRDQ: Chronic Respiratory Disease Questionnaire; CRDQ-D: dyspnoea domain of CRDQ; CRDQ-F: fatigue domain of CRDQ; PFSDQ-M: Pulmonary Functional Status and Dyspnea Questionnaire, modified version; FACIT: Functional Assessment of Chronic Illness Therapy.

Table 3. Patient-reported outcomes used in PR with an indication of the response to PR in general (or in subgroups)

Instrument name	Clinical application	Minimal important difference
St George's Respiratory Questionnaire	Assessment of HRQoL	4 points [45]
Chronic Respiratory Disease Questionnaire	Assessment of HRQoL	10 points (total score) [40]
COPD Assessment Test	Assessment of health status	2 points [46]
Hospital Anxiety and Depression Scale	Assessment of anxiety and depression	1.5 points [47]
Clinical COPD Questionnaire	Assessment of health status	Total score 0.4 [48]
PRAISE	Self-efficacy for PR	NA (but responsiveness to PR demonstrated) [49]
Lung Information Needs Questionnaire	Evaluation of respiratory education needs	NA (but responsiveness to PR demonstrated) [50]
Bristol COPD Knowledge Questionnaire	Evaluation of respiratory education needs	NA (but responsiveness to PR demonstrated) [51]

PRAISE: Pulmonary Rehabilitation Adapted Index of Self-Efficacy; HRQoL: health-related quality of life; NA: not available.

have little impact on self-efficacy, quality of life or functional outcomes in patients with COPD [55]. Potentially useful outcomes for evaluating the acquisition and effectiveness of self-management education include the Lung Information Needs Questionnaire (LINQ) [50], the Bristol COPD Knowledge Questionnaire [51] and the Health Education Impact Questionnaire (heiQ) [56]. Each has demonstrated responsiveness to PR; however, all are infrequently used in conventional PR programmes. Their importance and clinical utility may best be determined according to individuals' specific education and/or self-management needs.

The supportive interdisciplinary PR environment enables opportunity to implement and refine strategies to manage various ailments associated with chronic respiratory disease. This may involve addressing issues such as poor inhaler technique, improving therapy adherence, translation of exercise into daily life activities, relaxation strategies or airway clearance therapies. This supports a fundamental aim of PR, which is to promote ongoing self-management of a chronic health condition. The precise strategies that best encompass "self-management" are not explicit, and require tailoring to individual needs. The breadth of potentially useful self-management strategies may include education/knowledge acquisition, action plans, goal setting, social supports and improvement to healthcare access (*e.g.* tele-health). The implementation of self-management strategies is not without controversy, however, as results from some prominent recent clinical trials have shown negative results [57], possibly attributable to a sense of "overconfidence" in patients' perception of their ability to self-manage their condition. It is also important that outcomes of self-management interventions are carefully interpreted in order to make accurate judgements of their effectiveness. For example, the adoption of action plans has been shown to increase healthcare utilisation and ICS use, potentially *via* increased recognition of the early signs of impending exacerbations [58, 59]. Contrary to common interpretation, such findings may represent positive outcomes in the context of self-management due to proactive activation of health-promoting behaviours. Instruments evaluating self-management skills and confidence, while not commonplace in PR programmes to date, may therefore play an important part of

PR assessments in determining the extent to which patients can accurately identify their ability to independently manage their disease.

Measurement of the impact of PR on self-efficacy can be made in a general context (*e.g.* global self-efficacy) or in the context of efficacy for a particular activity (*e.g.* participation in physical activity or exercise). Examples of outcomes that may be useful in PR include the Self-Efficacy Scale [60], COPD Self-Efficacy Scale, Stanford Self-Efficacy for Managing Chronic Disease Scale and the Pulmonary Rehabilitation Adapted Index of Self-Efficacy (PRAISE). The latter was developed specifically for application in a PR context and contains items relating to both "general" self-efficacy and self-efficacy specific to PR (challenges faced by PR attendees). It does not, however, evaluate some important aspects targeted during PR, such as motivation for undertaking exercise, desire to become physically active and patient satisfaction. Specific motivation to exercise can be best assessed by either questionnaires (*e.g.* the self-regulatory questionnaire for exercise (SRQ-E)) [61] or from a simple therapist/patient interview assessment conducted both at baseline and, ideally, during the PR programme. Despite not being designed or validated specifically for patients with COPD, the SRQ-E has been applied to investigate intrinsic motivation for undertaking physical activity [62]. Its use in the context of PR still lacks validation; however, measurement of self-efficacy could be an important indicator of the long-term success of a PR programme if it provides insight into the potential for translation into daily life activities (*e.g.* increasing daily physical activity levels), particularly those aligned with patient goals. Little attention has been given to this aspect of research in PR.

Evaluation of nutritional status

Assessment of nutritional status and its trajectory of change during PR is an important but commonly overlooked component of patient assessment. Ideally, a routine clinical investigation with a dietician is recommended upon PR admission to ensure patients with abnormal body composition and/or suboptimal dietary habits are targeted for nutritional interventions. It would also help verify the presence of any acute changes in body weight prior to commencing an intervention, which may in turn relate to training responses. Although specific dietary screening tools do not exist for patients with COPD, assessments such as the BMI (body weight$\times$height^{-2}) and bioelectrical impedance (which will be described in this section) to assess body composition are now more routine in clinical practice. The use of BMI alone can, however, result in patient misclassification. For example, identification of a tall patient as a "low" BMI despite a lifelong history of a healthy ectomorph (thin) body type, or identification of a short patient as a "high" BMI despite a usual mesomorph (muscular) body type. However, in combination with more detailed information such as FFM (body lean mass+bone mass), it is possible to provide a nutritional risk profile that links findings with negative outcomes. For example, a model proposed by an ERS task force categorises patients into six groups defined according to BMI and FFM index (FFM$\times$height^{-2}). This model allows estimation of the potential for negative outcomes ranging from "impaired physical performance" to "increased mortality risk" [63].

While not a primary aim of PR, engagement with healthcare professionals during training sessions also offers opportunity for weight control measures to be implemented. Figure 2 shows data from the authors' institution in Leuven, indicating changes in body weight after 3 months of PR, relative to baseline BMI. Shaded areas indicate patients with suboptimal baseline BMI and "desired" (light grey) or "undesired" (dark grey) changes in body weight

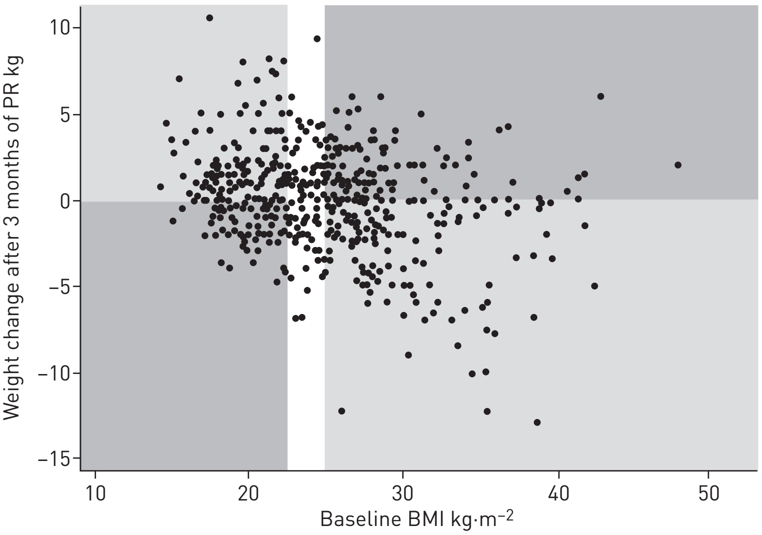

Figure 2. Effect of a 3-month PR programme on weight change. Shaded areas indicate patients who are either overweight (BMI >25 $kg\cdot m^{-2}$; right portion) or underweight (BMI <22.5 $kg\cdot m^{-2}$; left portion). Light grey areas denote "optimal" body weight responses; dark grey areas denote "suboptimal" body weight responses.

during the programme. The latter (dark grey) reflects a group who may benefit from more intensive nutritional support/interventions.

Two commonly used techniques to measure lean mass are bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DEXA) [64]. BIA is a portable and affordable tool that provides a reproducible measurement of body composition (FFM and fat mass). It has been validated for use in patients with COPD [65]. A disadvantage of BIA is the necessity for standardisation of the time of measurement and last meal composition. Furthermore, the electrical current used in BIA may interfere with the function of pacemaker devices, rendering it contraindicated in this patient subgroup. DEXA is a more sophisticated method that provides information about body composition and bone mineral density, which can be useful for patients on long-term corticosteroids [66]. This technique is less readily available in clinical practice and incurs high costs.

Evaluation of other relevant factors

In order to complete the comprehensive, personalised evaluation of patients who attend PR, the evaluation of other factors with potential to affect health change during the course of PR is important. Examples of such factors and possible strategies to evaluate them are listed in table 4. As standardised assessment tools rarely exist for such purposes, therapists should develop appropriate ways to evaluate such factors in conjunction with the unique goals and aims of PR patients.

When should the benefits of PR be assessed?

The benefits of PR should be assessed, at a minimum, at the end of the programme. Ideally, the effects should also be formally assessed during PR to enable adaptation of the

Table 4. Other factors requiring evaluation upon entry to PR programmes

Factor	Potential method of evaluation
Adherence to respiratory medications	Frequency of use of rescue medications; qualitative evaluation of inhaler technique
Anxiety/depression	Hospital anxiety and depression scale; the Hamilton anxiety rating scale and the Center for Epidemiological Studies Depression (CES-D) scale; medication use
Active/passive social support network	Evaluation of exposure to stressors in the home or community setting (*e.g.* social supports, relationship stress); psychological interventions

programme to better meet the needs of patients and ensure individual goals are attained upon programme conclusion. Little is known about the trajectories of change of conventional PR outcomes. It is likely not all benefits are obtained at the same pace. For example, achieving benefits in physical activity may take longer than the time taken to obtain physiological benefits [67]. ZuWallack *et al.* [68] demonstrated improvements in exercise endurance from session to session, but more rapid improvements in terms of health-related quality of life. The latter appeared to plateau after as little as four to eight rehabilitation sessions. Intermediate assessments can provide objective and often positive results of the rehabilitation programme to patients. This may in itself be a motivator to continue with the programme for individual patients. Clinicians need to find a balance between formal outcome assessment and providing the appropriate therapy. Formal assessments during rehabilitation programmes (*e.g.* midway evaluations) can be an effective strategy to titrate exercise therapy in accordance with patients' progress and changing needs. Alternative training forms can be adopted when the effectiveness of the training programme is lagging behind. In conjunction with session-by-session monitoring, this strategy can enable implementation of periodisation (alteration of volume, intensity and duration) to further maximise training effects [10].

It also seems reasonable to offer patients the opportunity for follow-up evaluation after PR. This can be particularly important as the post-PR period frequently represents a challenging time, requiring independent translation of “new” habits into daily life. Aims of such evaluations may include revision of goals, identification of support needs, monitoring the longevity of training effects (*e.g.* exercise capacity, skeletal muscle function, quality of life) and effect on healthcare utilisation. The exact timing of such assessments is likely to depend upon site-specific factors such as staffing levels and capacity.

Towards a standardised, comprehensive assessment of benefits

The field of PR is spoiled for choice of outcome measures to assess the benefits of interventions. Clinicians need to balance relevant outcomes and practical time investment to conduct all assessments. The assessment at the start of a programme may be more comprehensive than the assessment of benefits. The former needs to capture the phenotype of patients and guide the selection of components and exercise training strategies. The latter is needed to make an objective judgement on the obtained effects and redirect patients towards additional interventions or motivate patients to continue exercising and being physically active outside the walls of the rehabilitation facility.

In order to comprehensively assess the benefits of PR, we propose the use of a limited number of physiological outcomes to capture the benefits of the training programme. We would objectively assess skeletal muscle strength *via* a seated strain gauge and conduct a functional exercise test, such as the 6MWT, to identify improvements in walking. We would also conduct an endurance exercise test, preferably on a cycle ergometer. Importantly, a maximal incremental exercise test must first be completed to determine the ideal endurance test intensity at baseline and acquire information on exercise tolerance and exercise limitation. This does not, however, need to be repeated upon PR conclusion. Additionally, the transference of benefits into daily life should be captured in the domains of symptom improvement and physical activity. The former can be addressed with a questionnaire, while the latter can be easily assessed with accelerometers [69, 70]. It is also important to capture the benefits in terms of quality of life. The CRDQ and St George's Respiratory Questionnaire are the two most frequently used questionnaires in the field of PR. Depending on the phenotype of the patient, as identified at the initial visit (poor nutritional status, psychological symptoms, specific daily life issues or problems with self-management), the assessment of the benefits of the programme can be complemented with assessments in these fields. To answer specific research questions, other outcomes can be helpful to capture benefits or understand the mechanism of such benefits.

Assessment of the processes of rehabilitation

In addition to determining whether PR has measurable physiological benefits for individual attendees, it is also important that PR programme effectiveness is evaluated for other relevant stakeholders. In order to do so, feedback must be provided not only to individuals who attend PR (*i.e.* patients) but also to referring clinicians, healthcare providers and insurers/funding bodies. Several simple indicators may be useful for this purpose, many of which are routinely collected during rehabilitation programmes, but not routinely reported in the medical literature. These may include uptake and completion rates of PR (including number of drop-outs and associated reasons), within-session and out-of-session (*i.e.* home) therapy compliance, consumer satisfaction with PR (*e.g.* *via* survey-based methods) and programme cost-effectiveness (*e.g.* cost–benefit analysis, calculation of the number-needed-to-treat to derive clinical benefit).

It is also important that publications of clinical PR studies include clear reporting of site-specific programme factors to enable bench-marking against other PR programmes. Examples of such programme factors may include programme frequency (number of sessions per week), duration (number of weeks), training type (aerobic, strength, balance, *etc.*) setting (hospital, community), staffing (staff/patient ratio, experience, professional background), resources (availability of expertise or equipment) and financial remuneration (costs, health insurance rebate). The collection and use of such data can help identify the benefits of PR programmes for specific regions, and enables tailoring of PR programme components to specific clinical settings and individual needs. This information therefore forms an important component in the comprehensive evaluation of the true impact of PR programmes for specific COPD populations.

The patient case history

We propose that the following assessments are undertaken to ensure that the most important aspects of assessment are adequately assessed for our patient (Mr X, described in the case history at the beginning of this chapter), in terms of both the physiological effects of PR and their impact on daily life.

Determining the physiological effects of PR

As performed in our example, we would conduct repeated 6MWTs upon completion of PR to measure change in functional exercise tolerance, as this test is simple to conduct, responsive to PR and has a clearly defined MCID (at a group level) [18]. Improvements detected in these tests are of value to clinicians, allow adaption of the programme when needed and provide benchmark data on programme effectiveness. In addition, these tests may be motivators for patients to continue the effort of exercise training. Care would be taken to replicate the initial test conditions, including walking without the aid of the recently prescribed rollator. Because of its sensitivity to detect change following PR, we would also complement this with an endurance (time) test, performed on a bicycle with metabolic monitoring (preferred method) or indoor walking track. Quadriceps force would be measured isometrically *via* a seated strain gauge. As our patient had a low FFM and received nutritional support during PR, a repeated dietary intake interview conducted by a qualified dietician and re-assessment of FFM could be advised.

Determining the impact on daily life

The CRDQ could serve as a measure of health-related quality of life, while the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ) can be used to capture the benefits of PR on symptoms (dyspnoea and fatigue) during daily life activities. Physical activity monitoring for up to 7 days (minimum 4 days) [71] would be useful to highlight the benefits in terms of altered daily life patterns and guide further advice for the post-rehabilitation phase. No indications were present to assess anxiety or depression at baseline, so these factors were not re-assessed at discharge.

Other considerations

The observed improvement in lung function (150-mL increase in FEV_1) is large and may have influenced end-PR results. Assuming no significant changes were made to the patient's usual respiratory medications, this is probably reflective of a (positive) recovery process from the acute exacerbation (or better adherence to the medication regime). This improvement is not typically observed following PR and should not be an assumed consequence of the PR stimulus itself. In consideration of the increased risk of exacerbations following previous exacerbations [6], we would also closely monitor the patient's progress over the following 6–12 months in order to document the number of hospitalisations (or healthcare utilisation) related to respiratory illness. This would enable simple estimation of the broad impact of the PR programme on the individual and the local healthcare system.

Conclusion

There is currently no formal consensus regarding the precise type and format of assessments of the benefits of PR programmes. The strong physiological rationale underpinning exercise training suggests that, at a minimum, the effects of a programme on measures of exercise capacity and muscle function should be evaluated. The perceived effects of PR on the cardinal PROs of symptoms and health-related quality of life should also be assessed. Physical activity should be monitored to capture how benefits are translated to concrete increases in physical activity. Further assessment may be warranted to capture benefits in specific areas identified as problematic in the initial (baseline) assessment. This assessment is important to inform the patients and referring healthcare practitioners on their progress, monitor the overall quality of the programme and make an informed judgement on appropriate aftercare.

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Chapter 18

Measurable aspects of health status in clinical practice

Jan H. Vercoulen[1,2], A. Rogier Donders[3] and Jeannette B. Peters[1,2]

Case history: A 47-year-old female patient has COPD at Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II, and is underweight. She reports taking her medication. She works 3 days a week as a housekeeper. She does not do any sports activities ("too tired after work") but has adequate physical condition. When asked, she reports no problems in daily life: "everything is fine". But what do we really know about this patient? Is everything really fine? Are a disturbed lung function, being underweight and feeling tired after work her only impairments in health status?

Chapter summary: A detailed assessment of the many aspects of health status is a prerequisite for patient-tailored treatment. The assessment of a patient's physiological functioning is standard in clinical practice. However, health status is an overall concept that covers many other elements in addition to physiological functioning, such as symptoms, functional impairment and quality of life. The latter three are highly subjective phenomena, in which psychological processes (cognitions, emotions and behaviour) play an important role. Therefore, these aspects of health status and psychological processes can only be measured using (self-reported) questionnaires. Many questionnaires exist, each with their own strengths and weaknesses. To measure all aspects of health status, many instruments must be integrated, with each instrument measuring a different concept. This process should be driven by a conceptual framework and should be subsequently tested empirically. The outcome of these questionnaires can also be used as an intervention to motivate the patient to change their behaviour in order to optimise self-management. Implementing questionnaire use in clinical practice will enhance treatment selection and improve patient-tailored treatment.

COPD patients not only experience physiological disturbances, but also symptoms, functional impairments in daily life and impaired quality of life. The latter three are poorly related to the physiological disorders [1]. In light of the fact that COPD is incurable and progressive, there has been increasing focus on symptom relief, reducing impairment and improving quality of life in past decades [2]. Symptoms, functional impairment and quality of life can only be measured by self-report of the patient, as these are either highly subjective phenomena or involve patient behaviour [2–4]. Since the 1990s, an increasing number of studies have used questionnaires to measure health status and quality of life in COPD (figure 1).

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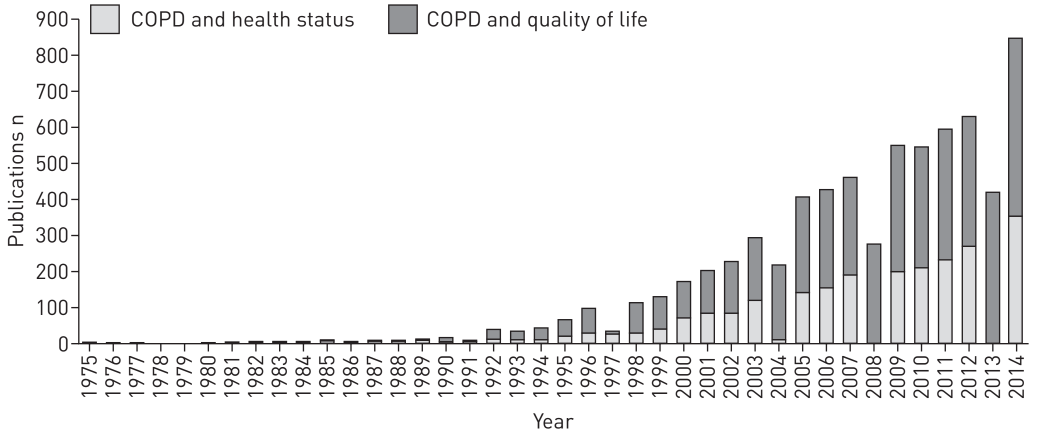

Figure 1. Number of studies on health status and quality of life in COPD per year since 1975 (PubMed search).

Questionnaires have a long tradition in psychological research and psychotherapy of quantifying subjective accounts in a standardised, valid and reliable way. These instruments were developed at the beginning of the 20th century and were first used on a large scale by the US Army during World War I in >2 million recruits to measure their mental capacity and suitability for leading positions [5, 6].

It is rarely recognised that the development and testing of standardised questionnaires is a science in its self and requires highly specific expertise. As early as 1997, a Round Table Conference of different stakeholders in the field of COPD research and clinical practice (including pharmaceutical and governmental representatives) concluded that at that time there was already an abundance of different instruments and that it was not clear which instruments would be best used; questions were also raised about the validity of these instruments [3]. The authors concluded that future research should focus on improving the validity of existing health status methods and instruments rather than developing yet more new instruments. In addition, from a clinical perspective, the interpretability of health status measures should be enhanced in order to be used in clinical care to help to tailor treatment to the individual patient's needs.

The aim of this chapter is not to provide a detailed review of all existing questionnaires (this can be found elsewhere [7–9]) but to discuss important patient-related concepts in COPD and describe (in line with the 1997 Round Table Conference) methods to integrate questionnaires and to improve their clinical applicability in order to enhance patient-tailored treatment.

Which concepts should be measured in COPD?

Questionnaires can be used to measure any concept that involves a subjective evaluation by the patient. For the sake of simplicity, we will divide these concepts into two main domains, each covering many subdomains. The first involves health status and the second involves psychological processes.

Health status

For anything that is not accessible directly by observation, such as heartbeat, a clear definition or conceptual framework is crucial [10, 11]. In the COPD literature, the terms health status, functional status, quality of life and health-related quality of life are used interchangeably. This is mainly due to the poor definitions of these concepts [11]. Consequently, over the course of different studies, this has led to multiple interpretations of the concept a specific questionnaire measures. This has not helped standardise instrument use in research and clinical practice, or elucidate which concepts(s) a specific questionnaire actually measures [12]. General health status theories make clear distinctions between these concepts, in which health status is viewed as an overall concept covering physiological function, symptoms, functional status and quality of life as conceptually distinct main domains [11, 13]. These main domains have been empirically shown to be subdivided into many more concrete relatively independent subdomains [14]. This means that each subdomain represents a unique aspect of a patient's health status.

Symptoms

In a recent American Thoracic Society (ATS)/European Respiratory Society (ERS) statement [7], dyspnoea, like pain [15], is viewed as a subjective experience that is derived from interactions between multiple physiological, psychological, social and environmental factors. The authors emphasise that dyspnoea *per se* can only be perceived by the person experiencing it. Therefore, dyspnoea can only be measured using a self-reported questionnaire. PARSHALL *et al.* [4] propose that instruments should be categorised into the three following dimensions. 1) Sensory perceptual, representing what dyspnoea feels like. 2) Affective distress, which measure the emotional aspects of dyspnoea. This may mean anxiety, but other emotions such as depression and frustration may also occur [16, 17]. 3) Symptom impact or burden, which measure how dyspnoea affects functional status.

Functional status

The terms functional status, functional capacity and functional performance are widely used [7]. Functional status can be defined as the individual's ability to perform daily activities. Functional capacity refers to the person's maximal potential to perform activities. Functional capacity can be measured using maximal ergometry testing, for example. This must be clearly distinguished from functional performance, which refers to what a patient is actually doing in daily life, and therefore reflects actual behaviour (*i.e.* physical activity). In general, patients with COPD are found to be rather inactive [18–21]; however, in our clinical experience, some patients may structurally over-exercise. Physical activity is one of the concepts studied extensively in COPD; a PubMed search found >2000 studies that considered this area. A detailed review of the literature in this respect can be found elsewhere [7]. However, most studies focussed on the relationships between physical activity and a wide range of other concepts, such physiological processes, prognosis and mortality, and considered physical activity as an outcome measure in intervention studies. In this section we will focus on the assessment of physical activity.

Physical activity in daily life has been defined as the totality of voluntary movement produced by the skeletal muscle during every day functioning [22]. Questionnaires have not proved to provide an accurate measure of actual physical activity [23–25]. This was also found with the Activity subscale of the St George's Respiratory Questionnaire (SGRQ), which showed only moderate correlation with an accelerometer [26]. One of the reasons for the poor performance of questionnaires in this respect is the fact that questionnaires connect with subjective processes and reflect a person's cognitive and emotional experience of their physical activity level, rather than their actual activity level [27]. Nevertheless, a patient's perception of physical activity is also important. It has been shown that a combination of patient-reported activity questionnaire and accelerometry provides more information on physical activity than each measure alone [28].

The only valid measure of actual physical activity is the accelerometer, which has been introduced into COPD research in recent years [29–31]. However, from a clinical point of view, the overall day or week activity level itself may not be the most important factor in COPD; how an activity is performed may be more crucial. For example, does the patient employ adequate energy-saving techniques, such as lowering tempo and intensity of his pace and taking periods of rest earlier? To measure such subtleties and nuances in activity requires highly sophisticated accelerometers.

Quality of life

This concept may be the most subjective of all and cannot be viewed as one single construct. In its essence, quality of life can be defined as a person's satisfaction with many different aspects of their life, such as housing conditions, financial situation, the quality of relationships (spouse, family, friends, colleagues), work, health and activities in daily life; it can also be taken generally as satisfaction with life as a whole [11]. Within this domain, many instruments have made incorrect claims of measuring quality of life, whilst in fact these instruments did not measure any aspect of satisfaction, but merely symptoms or functional status [14, 26]. For example, in many studies, the SGRQ has been referred to as a measure of quality of life [32–37]. Daudey *et al.* [26] showed that the SGRQ measured subjective symptoms and subjective impairment, but did not measure any aspect of quality of life as conceptually defined in the present paper.

Psychological processes

In 1977, Engel introduced the biopsychosocial model into medical science [38]. In addition to the biomedical aspect, this model incorporates the psychological, social and behavioural dimensions of a disease. As humans we are not passive perceivers of the world around us. External stimuli and events are processed psychologically on a cognitive and emotional level, which influences the person's behaviour. Cognitive processes refer to any idea a person has about the world around them. Illness cognitions refer to any specific cognition the patient has in relation to their disease [39, 40]. Examples are: interpretation of bodily sensations; ideas about cause and effect; expectations about the future; self-efficacy expectations (sense of control); *etc.* Cognitions are very potent in inducing specific emotions and behaviour. Bodily sensations, such as chest tightness, may be interpreted as dyspnoea and some patients may interpret this as danger (cognitive level). Such cognitive interpretations may trigger anxiety (emotional level) and avoidance of situations (behavioural level) that the patient thinks (cognitive level) cause dyspnoea. The environment (partner, friends, colleagues, the doctor, media and the internet) may influence the patient's cognitions. In this respect, cognitive and emotional processes are important determinants of self-management behaviours [41]. Examples of adequate self-management behaviours are adherence to medication regimens, exacerbation management, adopting a healthy lifestyle (regular exercise, balanced dietary intake, smoking cessation), energy-saving strategies, breathing regulation, stress management, *etc.* Many questionnaires and assessment methods have been developed and published in psychological science to validly measure different psychological processes.

Questionnaires: psychometric properties

Two central aspects of the usefulness of questionnaires are reliability and validity.

Reliability is defined as the proportion of observed variance that can be attributed to true score variance. As such, the reliability of a questionnaire is directly related to the heterogeneity of the population in which the questionnaire is to be applied. When a given questionnaire is administered in a homogeneous population (with almost no differences between true scores), the variance in observed scores only reflects the amount of measurement error. Since it is assumed that the measurement error is a property of the questionnaire, this implies that the reliability will increase when the questionnaire is administered in a more heterogeneous population. Thus, estimates of reliability should always be evaluated with acknowledgement of the population in which the estimates were obtained; when a reliability of 0.8 is reported for the general population, it should be acknowledged that the reliability might be lower when the questionnaire is administered in a patient population [42]. There are several methods of estimating the reliability, including test–retest and internal consistency.

Validity relates to whether the questionnaire measures what it is supposed to measure. Since this is a broad definition, a myriad of different approaches to determining the validity of questionnaires has been developed. However, the modern approach to validity is characterised by a focus on the application. One should not worry about whether a questionnaire is valid in general, but whether a questionnaire is valid in a given application [43, 44]. If a questionnaire is intended to provide a prediction for a certain concept, the validation study should result in an estimation of how well the questionnaire can predict the criterion. If a questionnaire is intended to replace an existing questionnaire, the validation study should look at the agreement between the two scales. Thus, the intended use dictates the type of validation study that should be performed. Notably, if a questionnaire is intended as an outcome measure in a trial, the validation study should investigate whether the questionnaire is sensitive to a change in the true score of a patient; moreover, it should be determined how large a change on the questionnaire corresponds to a minimal clinically important difference. Viewed in this manner, one can only conclude that many "validated" questionnaires are misused, since the validation study was aimed at different aspects other than the intended use.

Enhancement of questionnaires for use in clinical care

In recent years, the increasing awareness of the major heterogeneity in COPD and its clinical manifestations has put more emphasis on multidimensional health status assessment as a prerequisite of enhanced patient-tailored treatment [45, 46]. The health status domains symptoms, functional impairment and quality of life consist of many subdomains [4, 11, 13, 14]. Patient-tailored treatment therefore requires a detailed assessment of a patient's health status, covering these subdomains. Therefore, integration of health status questionnaires is required, which involves combining instruments that each (validly) measure different subdomains into a battery of instruments. In addition, most health status instruments were originally developed for research purposes and have many practical limitations to applicability in standard care.

Integration of questionnaires

There have been many studies that have compared existing instruments, in which the favourable outcome was commonly that both instruments measured the same concept [47–52]. However, in the process of integrating questionnaires to provide a detailed picture of health status, we are not looking for instruments that measure the same concept but for instruments that measure different concepts. In recent years, studies have focussed on the SGRQ, the COPD Clinical Questionnaire (CCQ) and the COPD Assessment Test (CAT), and have found high inter-correlations between these three instruments [53–55], suggesting that they measure the same concepts of health status. Thus, the short CCQ or CAT could be used in preference to the longer and more complicated SGRQ [56].

However, this type of study does not provide information about what concepts are actually being measured [26, 57, 58]. For example, the subscale structure of many instruments does not always reflect the underlying concepts that are actually being measured by these instruments. The SGRQ contains three subscales, but one study found evidence of a unidimensional structure of the SGRQ [58]. The CCQ also contains three subscales, but evidence was found of only two underlying concepts: "general impact" and "cough" [57]. This mismatch between the subscale structure and the actual underlying conceptual structure is often the result of the fact that the development of health status instruments was not based on a conceptual framework [12], let alone that this underlying conceptual structure has been tested empirically.

It is not only the development of questionnaires that should be based on a conceptual framework and subsequent empirical testing [11, 59, 60]; this approach should also be applied to the integration of instruments. Conceptual framework means: a conceptual definition of the main domains and their subdomains, and the questionnaires used to measure these subdomains. We could only find two studies in COPD that attempted an integration of existing instruments using a conceptual framework.

The first study [61] linked the items of 11 COPD-specific questionnaires to categories in the International Classification of Functioning, Disability, and Health (ICF) framework [62] using expert opinion. Despite major variability of items between the instruments, it was shown that there was a major overlap in the concepts measured by these instruments: from a total of 339 items, only 21 were unique to a specific instrument. Although this approach helps us to gain more insight into which concepts are measured by individual items, no empirical integration of instruments was performed nor did this study provide information about the psychometric properties of the instruments studied [61].

The second study was not only based on a conceptual framework but was also subsequently tested empirically [14]. To illustrate this approach, figure 2 presents a schematic of the procedure and results with respect to the main domain, functional impairment. Based on theoretical models and clinical considerations, the main domains and subdomains of health status were first defined conceptually (figure 2). These conceptual models guided the selection of instruments to measure these concepts. Subsequently, the models were tested empirically in a group of stable outpatients with COPD. Hence, the definitions of health status main domains and subdomains were more based on empirical data than definitions found in the literature (figure 2). This approach also provided a new type of validity information on existing instruments, in which exploratory factor analyses played a central role. In these analyses, instruments are organised into a factor structure based on the underlying concept they measure (figure 2).

In a previous study, we used this framework as a guide to integrate instruments into a battery of instruments, called the Nijmegen Clinical Screening Instrument (NCSI), which provided a detailed assessment of health status but was short enough to be used in daily care [17]. As each factor represented one single concept (subdomain), one instrument

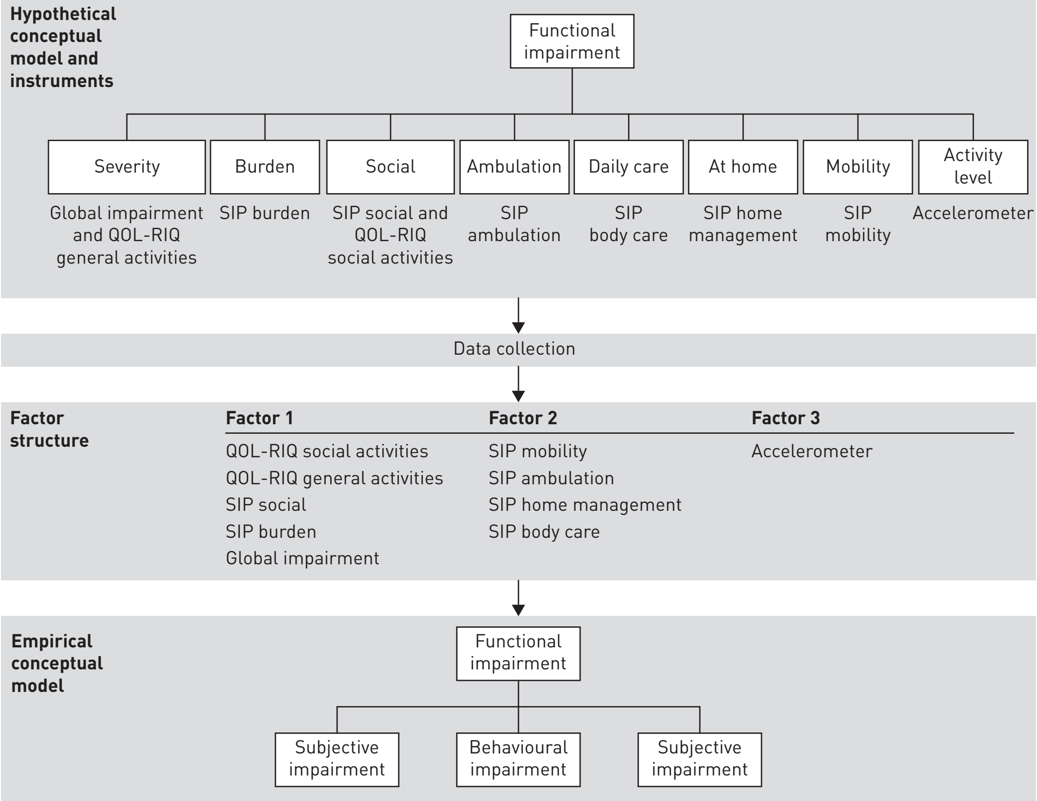
Hypothetical conceptual model and instruments
Functional impairment
Severity
Burden
Social
Ambulation
Daily care
At home
Mobility
Activity level
Global impairment and QOL-RIQ general activities
SIP burden
SIP social and QOL-RIQ social activities
SIP ambulation
SIP body care
SIP home management
SIP mobility
Accelerometer
Data collection
Factor structure
Factor 1
QOL-RIQ social activities
QOL-RIQ general activities
SIP social
SIP burden
Global impairment
Factor 2
SIP mobility
SIP ambulation
SIP home management
SIP body care
Factor 3
Accelerometer
Empirical conceptual model
Functional impairment
Subjective impairment
Behavioural impairment
Subjective impairment

Figure 2. Schematic presentation of procedure and main results with respect to the main domain, functional impairment. QOL-RIQ: Quality of Life for Respiratory Illness Questionnaire; SIP: sickness impact profile.

included in a specific factor was sufficient to measure that concept, the rest were redundant. In general, we chose the shortest instrument from each factor. It is imperative to note that the NCSI is not a new instrument, but merely an empirically composed battery of existing instruments, enabling a detailed but short assessment of health status.

In addition to the studies described above, our study also showed that questionnaires do not always measure the concept we expect them to measure based on face value (*i.e.* the item content) [14]. In fact, a very interesting phenomenon was observed, the so-called methods variance effect. This means that scores of a particular instrument are not only dependent on the concept assumed to be measured but also on the method of assessment that was used [63, 64]. In the functional impairment model, the factor structure was not based on grouping instruments with the same item content but on grouping based on the dimension subjectivity–objectivity. Factor 1 contained instruments that by item content were expected to measure different activities, social functioning, experienced burden of impairments, and problems with daily care, and thus would not have been expected in the same factor (figure 2). What the instruments in factor 1 do have in common is that the item-and-response format requires highly subjective and general interpretations. In contrast, the instruments in factor 2 require simple responses (yes or no) to very specific and concrete activities or situations. These instruments are therefore more related to actual behaviour and are, thus, more objective. Actual physical activity contains an accelerometer, which is the most objective measure of behaviour. Questionnaires with an item-and-response format requiring highly subjective interpretations of the patient are more likely to measure a general notion of being ill, also referred to as "illness perceptions" or "illness cognitions" [39, 40].

Questionnaires as a tool to improve patient care

Improving the practical usability of questionnaires

An instrument or a battery of instruments has to meet the following criteria to be suitable for use in standard care [17]. 1) The assessment should provide a detailed picture of a patient's health status. As discussed in the previous paragraphs, this requires the integration of different questionnaires. 2) The instrument has to be as short as possible to reduce unnecessary burden on the patient and on the healthcare provider. In this respect, special attention has to be paid to the removal of any redundancy in the battery. 3) Questionnaire completion, scoring procedures and data management should preferably be automated. Nowadays, websites and smartphone apps are booming in healthcare, and are commonly applied in telemonitoring and self-management support [65, 66]. 4) Scores have to be clinically meaningful on the level of an individual patient. Adequate normative data are of the utmost importance to enable patient-tailored treatment, as normality cannot be defined by the absence of symptoms or functional impairment. Healthy people can experience symptoms like fatigue and shortness of breath as well. Normal ageing also introduces impairments into daily life. Therefore, normative data from adequate control groups must be collected to determine the cut-off between normal scores and abnormal scores for each instrument.

Instruments such as the CAT and the CCQ were specifically developed to provide a quick health status assessment (criterion 2). However, both instruments only measure one or two subdomains of health status [26, 56–58], and therefore do not provide a detailed assessment of health status (criterion 1). The CAT and the CCQ lack automated questionnaire completion, scoring procedures and data management (criterion 3), and do not have empirically derived normative data (criterion 4). The NCSI battery fulfils all criteria, although questionnaire completion takes more time (15–20 min) than with the CAT and the CCQ (criterion 2). The NCSI provides a detailed assessment of health status, measuring 22 subdomains (criterion 1). Questionnaire completion, scoring and data management are fully automated by a web application, which also allows questionnaire completion at home (criterion 3). Results are presented automatically by the graphical PatientProfileChart (figure 3), on which the score range for each subdomain is divided into normal (green), mild (yellow) and severe (red), based on data from different control groups. The scores of the subject discussed in the Case history at the beginning of the chapter are presented in figure 3. It is very clear from her PatientProfileChart that she experiences more health status problems than could be identified with physiological assessment or from her self-report during the consultation.

Health status instruments enhancing patient-tailored treatment

Studies have begun to emerge that evaluate the ability of existing questionnaires to enhance patient-tailored treatment; for example, by aiding the communication between the physician and the patient [17, 67–69]. An early study using the five-dimensional Quality of Life for Respiratory Illness Questionnaire (QOL-RIQ) in primary care showed that impairments in health status were significantly related to subsequent general practitioner interventions [69]. Physical complaints were positively associated with changes in medical prescriptions and with education about control regimens. Emotional complaints were

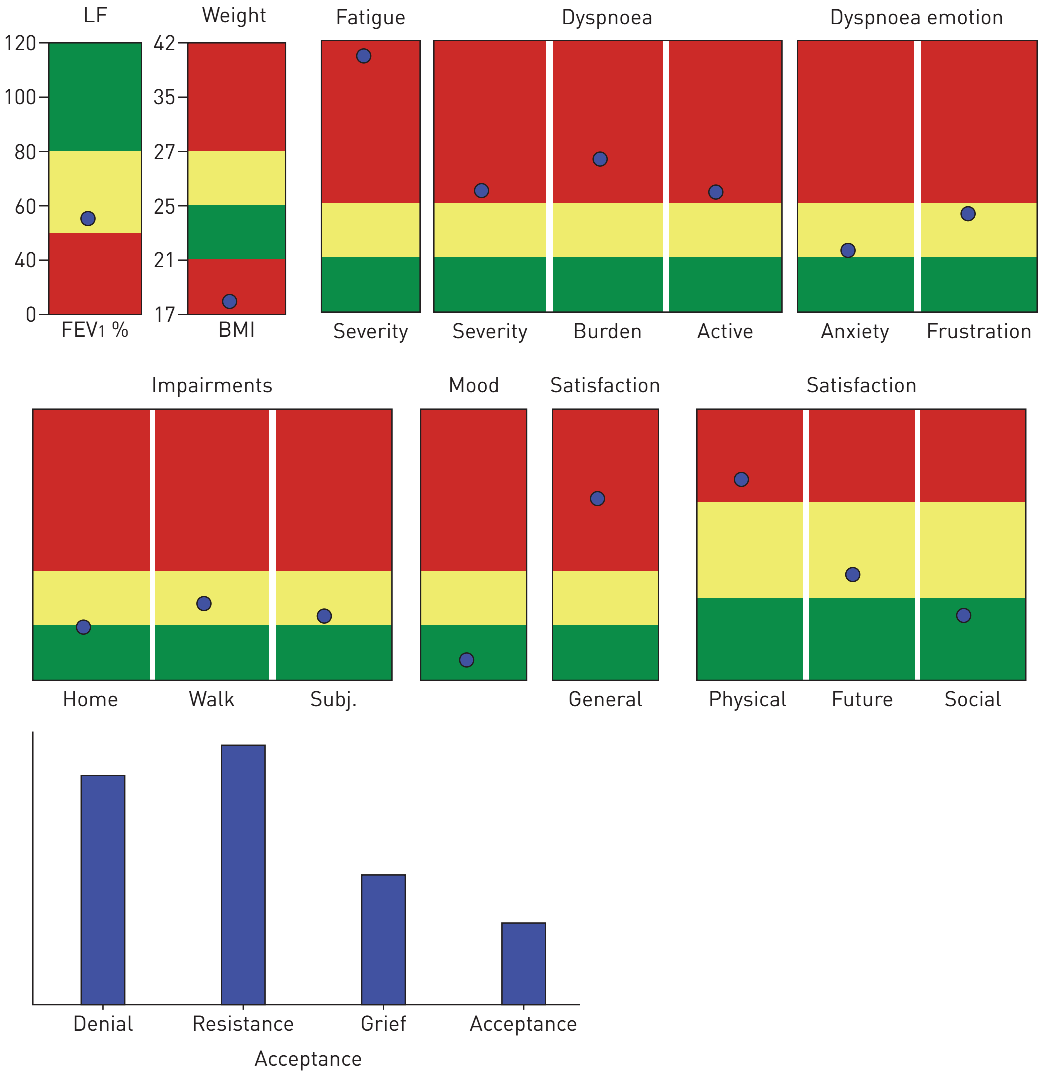

Figure 3. The PatientProfileChart: a graphical presentation of results of the Nijmegen Clinical Screening Instrument. The dot represents the score of the patient. Green: normal functioning; yellow: mild problems; red: severe problems. LF: lung function; Subj.: subjective. Reproduced and modified from [67] with permission from the publisher.

related to additional follow-up visits and counselling. Another study investigated the impact of the CAT on the quality of primary care consultations in a two-arm design: consultations with the CAT *versus* consultations without the CAT [68]. The only significant impact of the CAT related to a better understanding by the physician of COPD-specific symptoms, such as breathlessness. No significant differences were found between the arms with respect to identifying depression, understanding the patient or overall performance [68]. In contrast, one study found high agreement between CCQ scores, scores of treating clinicians and scores of reviewing clinicians [70]. From this perspective, one might wonder what the added value of the CCQ is. Other papers on the CAT, SGRQ and CCQ merely address the possibility of using questionnaires to enhance patient-tailored treatment [70–72] or present the protocol of an ongoing study [70].

The NCSI is not only an assessment instrument but also incorporates an integrated intervention. The NCSI intervention involves a semi-structured discussion of the PatientProfileChart (figure 3) with the patient and the patient's spouse/partner. The PatientProfileChart makes it very simple for the patient and for the caregiver to actually see the type and severity of health status problems. In addition, this discussion elucidates the underlying causes of these problems, particularly the role of the behaviour of the patient. Both aspects enable the formulation of patient-tailored treatment goals and increase the patient's motivation to adopt more adequate self-management behaviours. This intervention and the psychological underlying mechanisms have been described in detail elsewhere [67].

Conclusion

Health status instruments provide an important supplement to traditional physiological measures. Health status is an overall concept covering physiological functioning, symptoms, functional impairment and quality of life as the main domains. As these main domains consist of many concrete subdomains, a detailed assessment of health status is a prerequisite to enhance patient-tailored care. However, currently, there is a trend to use one single instrument in clinical practice, mainly the CAT or CCQ. These instruments measure only one or two aspects of health status. In addition, these instruments do not exactly measure the concepts they are assumed to measure. It seems that this current trend is drifting away from the necessity to integrate instruments to provide a detailed assessment.

In addition to assessment purposes, questionnaires have other promising applications. Patients with COPD are reportedly being viewed as poorly motivated to endorse adequate self-management behaviours [73]. This is one of the reasons why self-management programmes have been shown to be only marginally effective [74]. Using questionnaires as an intervention may be a promising tool to formulate patient-tailored treatment goals and to motivate the patient to change their behaviour.

Given the above, we think that the main conclusions of the 1997 Round Table Conference still have great actuality. Future studies on health status questionnaires should focus on: 1) clarifying which concepts a questionnaire actually measures; 2) empirical integration of instruments to provide a detailed assessment of health status; 3) developing interventions based on questionnaire results, which enhance patient-tailored treatment and increase the patient's motivation to adopt adequate self-management behaviours.

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Disclosures: None declared.

The role of telemedicine

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Case history: A male patient was diagnosed with COPD by his primary care physician, who confirmed moderate airflow limitation using spirometry. His main complaint was of progressive dyspnoea. He was referred for teleconsultation by his primary care physician, which involved attendance at a local medical clinic where he was interviewed by a respiratory physician located at a large medical centre 60 miles away. His medical chart, cardiogram, spirometry and chest radiograph were forwarded to the respiratory physician. During the consultation, he was advised to stop smoking, receive regular influenza vaccinations and maintain his activity levels. The patient complained of reduced exercise tolerance and said he was becoming housebound. Although a large rehabilitation programme was operational at the main health centre 70 miles away, a small satellite six-person programme was available at a neighbouring community centre. Following referral to this programme, the patient underwent a telemedicine assessment. Once enrolled, he received online lectures in real time, simultaneously with the main rehabilitation programme. He undertook onsite exercise training supervised by a healthcare professional who was linked in real time to the physical therapist at the main centre. Following programme completion, he was followed up *via* teleconsultation with the nurse coordinator at the central site.

Chapter summary: Telemedicine, the provision of healthcare at a distance, is a novel approach to the management of individuals with COPD, driven by the need to facilitate access to healthcare for patients living in geographically remote regions and communities. Telemedicine applications may involve teleconsultation, telemonitoring, telehealth and telerehabilitation. Telemedicine may facilitate the early detection and management of a clinical deterioration. It aims to improve patient self-monitoring and can be used to provide patient education and rehabilitation. While patient attitudes towards this model of healthcare delivery are generally positive, the clinical benefits of telemedicine in COPD are variable and the cost-effectiveness of these interventions has not yet been determined. Despite mixed results, a select group of patients with COPD appear to benefit from differing models of telemedicine.

According to global population-based studies, the rising prevalence of COPD, particularly in those aged ⩾65 years [1], is associated with a significant social and economic burden worldwide [2, 3]. The greatest proportion of expenditure is due to hospital costs for patients admitted with AECOPD [4, 5], with a readmission rate of 63% over 1 year in those with severe disease [6]. As the severity of COPD impacts on healthcare-resource utilisation, providing early and effective healthcare management is essential to slowing disease progression, improving health-related quality of life (HRQoL)

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and reducing the disease's economic impact [7–9]. Traditional models of care delivery may struggle to provide an adequate service. This, coupled with changing health expectations and international concerns around healthcare budgets, has driven the need for a healthcare transformation, which includes the use of telemedicine.

Telemedicine aligns with health policy to provide convenient, safe care as locally as possible [10–12]. The combination of technology, telecommunications and informatics enables healthcare to meet innovation.

In this chapter, we describe what telemedicine involves and how it might be applied in COPD. We will discuss the evidence of the applications and the attitudes of consumers. Practical elements of telemedicine will be outlined.

The taxonomy of telemedicine

Telemedicine is broadly defined as medicine practiced at a distance [13]. It is an umbrella term that refers to all systems and modalities that use electronic communication and information exchange to deliver healthcare services to individual patients who are at a different geographical location to the healthcare provider [14]. Telemedicine encompasses a range of services, including teleconsultation, telemonitoring, telehealth and telerehabilitation (figure 1) [14].

Teleconsultation

Teleconsultation is real-time consultation between patients and healthcare practitioners (HCPs) or between two or more HCPs *via* network, video conference technology or

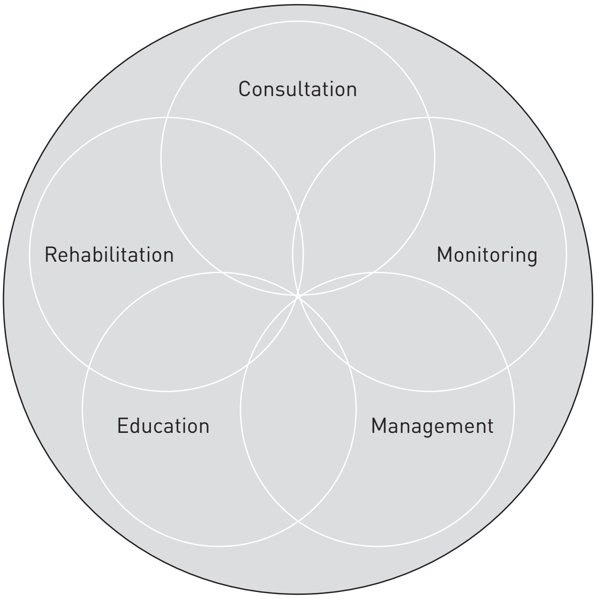


Figure 1. The taxonomy of telemedicine.

telephone [10, 15, 16], enabling patient consultation and ongoing medical management to occur through synchronous interaction [17, 18]. The patient may undertake the consultation at their local healthcare centre or at home. Virtual communication between physicians in other healthcare institutions facilitates patient-related specialist consultation and case conferencing in distant communities [18]. Both forms of consultation are supported by the electronic transfer of relevant medical images, health records and laboratory results.

Telemonitoring

Telemonitoring is the remote exchange of data collected from patients within their place of residence; this data is then transmitted to a HCP at a central location *via* telecommunication [10]. Information may be collected automatically or require action on the patient's behalf [13], with the interaction being synchronous or asynchronous (such as the storing and forward transmission of data) and performed using instant messaging, e-mail or web-based consultation. The electronic transmission of data enables regular interpretation of the patient's current status by a HCP. The process is illustrated in figure 2, with an example of the steps involved in monitoring outlined in figure 3. Telemonitoring enables patient support, clinical decision-making by the HCP and the initiation of management strategies to provide remote yet individualised healthcare [15, 19–21].

Telehealth

The term telehealth has often been used interchangeably with telemedicine. Telehealth extends the scope of teleconsultation and telemonitoring to a broader set of activities including patient education and counselling. Telehealth can include primary prevention and early detection of COPD, through remote spirometry, as well as guidance for smoking

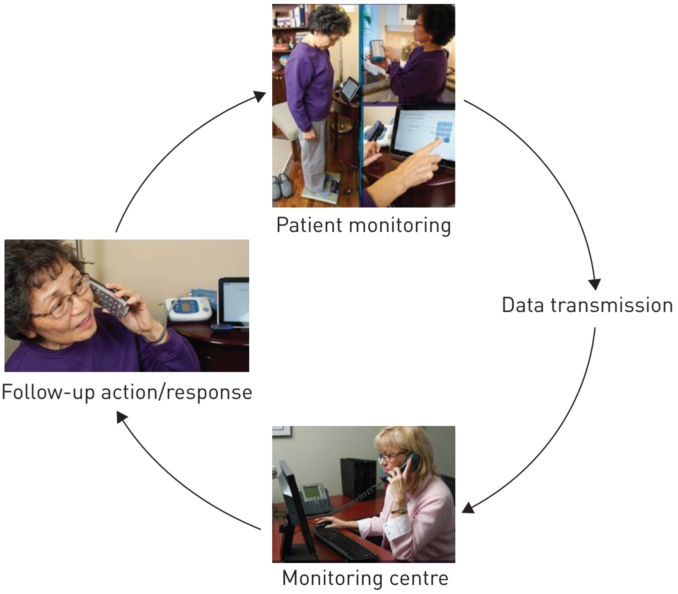
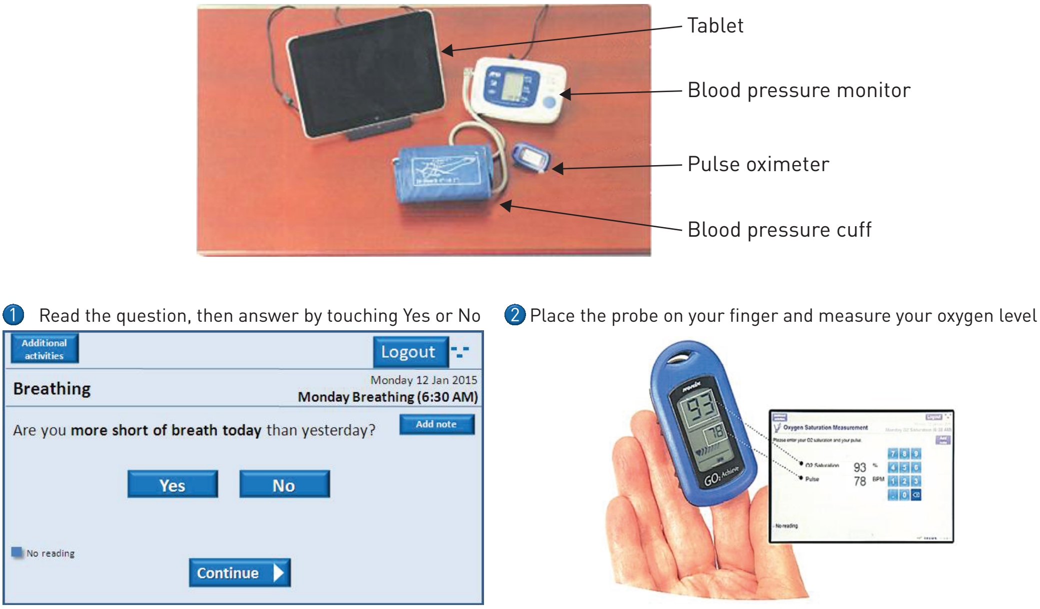


Figure 2. The process of telemonitoring. Photographs reproduced with the kind permission of the Ontario Telemedicine Network (Toronto, ON, Canada).



① Read the question, then answer by touching Yes or No

Breathing

Monday 12 Jan 2015

Monday Breathing (6:30 AM)

Are you **more short of breath today** than yesterday?

② Place the probe on your finger and measure your oxygen level

Figure 3. An example of telemonitoring of respiratory status. Photographs reproduced with the kind permission of the Ontario Telemedicine Network (Toronto, ON, Canada).

cessation, education programmes, strategies to encourage adherence to medication and other treatments and support for self-management [13, 22–24].

Telerehabilitation

Telerehabilitation is the provision of rehabilitation services at a distance using telecommunication technology as the service delivery medium [25]. Telerehabilitation services may be delivered by a number of health disciplines, with rehabilitation training provided to patients at a satellite clinic or at home [26, 27].

Despite the separate domains of telemedicine, hybrid approaches (*e.g.* teleconsultation with telemonitoring) are often applied in COPD. Overall, the interaction between electronic communication and information technology with various human/technological interfaces facilitates medical consultations, means a patient's condition can be monitored, and enables the prescription of treatment [18, 28]. It enables a healthcare shift from an institutionalised, fragmented and episodic approach to an integrated, team-based and patient-centred model (table 1).

Practical requirements for telemedicine

Key elements necessary for the implementation of telemedicine include information and communication systems [29], with the exact requirements depending on the intervention's goals. Modes of telemedicine can be achieved with the use of an active and reliable landline, cell phone technology or satellite link, depending on the patient's location. More sophisticated approaches use computer technology (tablet or desktop), video conferencing with a webcam and microphone, or peripheral medical equipment, such as a pulse oximeter

Table 1. Healthcare shift towards telemedicine

Moving from:	**Towards:**
Provider orientated	Patient centred
Information silo	Team based
Fragmented	Integrated
Episodic	Information/data rich
Bricks-and-mortar-centric	Ubiquitous access to healthcare services
Expensive	More efficient

or stethoscope, which may be connected through Bluetooth adaptors. Complex models use broadband or wireless technology for information and telecommunication transmission.

Monitored patient information in telemedicine for COPD

Various cardiorespiratory signs and symptoms are monitored in real-time by the individual patient as part of telemedicine. Table 2 outlines the most common types of physiological data that are collected and transmitted. The collation of clinical symptoms is derived from questionnaires [30, 34–36]. The collection of physiological information may require the patient to wear equipment (short- or long-term) that enables considerable information to be accessed [37].

The frequency of monitoring varies among the studies; from as much as five times [37], three times [38] or twice a day [30], to daily monitoring [33, 34, 37, 39–47] or twice a week [48]. Selected studies monitored physiological signs [33, 34, 38, 44, 46, 47], symptoms [41, 42] or a mixture of both [30, 39, 40, 43]. Currently, there is a lack of consensus as to which information should be tracked to best reflect a patient's clinical status [49, 50].

Table 2. Physiological and clinical information assessed during telemonitoring

Cardiovascular signs
  Heart rate, blood pressure, ECG, weight
Cardiovascular symptoms
  Increased ankle swelling
Respiratory signs
  S_{pO_2}, respiratory rate, auscultation, spirometry, PEF
Respiratory symptoms
  Change in sputum colour, quantity and viscosity, increased cough, increased dyspnoea or wheeze, sore throat
Other signs or symptoms
  Temperature
  Ability to complete usual daily activities
  Fatigue

S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; PEF: peak expiratory flow. Data from [30–33].

Establishing baseline parameters in telemonitoring

Baseline values for physiological signs and symptoms are monitored for their trends and oscillations during a period of clinical stability. This information provides a reference to help detect abnormal excursions in these parameters, which could be indicative of an AECOPD [32, 45, 51] or an individual patient's usual variation (figure 4). On the basis of this, a triage system is established, with red alerts indicating measures falling below the normal threshold levels [37, 53]. In the event of a red alert, a clinical response is implemented by the HCP according to a set protocol established for the individual patient [45]. This system may incorporate HCP contact with the patient to confirm symptoms and gain more information prior to commencing treatment [33, 45].

Ideal candidate with COPD for telemedicine

Suitable candidates for telemedicine have key characteristics. The individual needs to be cognitively intact, with an ability to understand and use the necessary technology. Effective communication skills in the language of the system are necessary to facilitate discussions with a HCP. If the candidate is unable to communicate (*e.g.* a patient with a tracheostomy), a reliable caregiver or family member is required to facilitate the individual's engagement with telemedicine. The candidate should demonstrate a willingness to undergo training and accept the provided technology, and should be reliable in their correspondence and transmission of information.

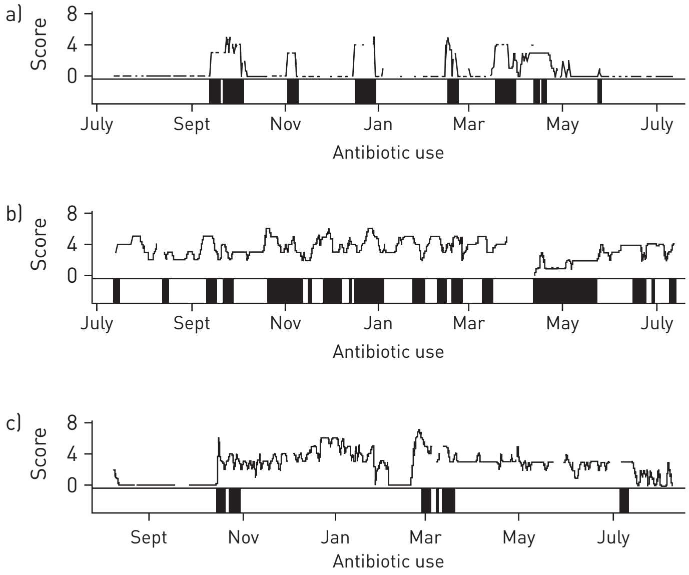


Figure 4. Classification of the patterns of AECOPD, showing antibiotic usage and symptom score (a higher score indicates worse symptoms). a) A long duration with minimal symptoms and occasional flares, most treated with antibiotics. b) A rolling pattern of symptoms, with frequent, almost continuous, high-level symptoms, and frequent antibiotic courses. c) An over-ridden pattern with frequent symptoms, few treated with antibiotics. Reproduced and modified from [52] with permission from the publisher.

Evidence of the role of telemedicine in COPD

Effects of telemedicine in patients with stable COPD

The effects of telemedicine in COPD have been explored in numerous studies and systematic reviews, with diversity in the applied models [15, 21, 49, 50, 54, 55]. Centres used telephone support [56, 57], home visits [58] and self-management education [59, 60]. Several studies incorporated video conferencing and the regular transmission and interpretation of the patient's clinical information by a HCP, who initiated action plans as necessary [30, 35, 37–40, 42–47, 61–67]. Others included regular teleconsultation with a HCP (nurse or physician) to provide patient advice, discuss treatment and review current status [11, 66, 67].

With respect to health-related outcomes and healthcare utilisation, the results of these models have been mixed. Systematic reviews that compared different approaches (telephone support and/or telemonitoring) to usual care found a lower rate of overall hospitalisation with telemedicine (OR 0.46 (95% CI 0.33–0.64)) [21, 50], but there was no difference in the number of hospitalisations caused by an AECOPD [21, 50, 68]. One review found fewer emergency department visits compared with usual care [21]; in contrast, another review found no between-group differences in the rate of emergency room visits [50]. The impact of telemedicine in reducing the number of hospital bed days varied between studies [15, 50]. The few studies that reported the frequency of visits to a specialist, or general practitioner or other HCP home care visits found mixed results [15, 46, 69–71]. The evidence is inconclusive for HRQoL; the different instruments used among studies limited their comparisons [50, 72]. Overall, telemedicine approaches that incorporated telemonitoring (of physiological signs and symptoms and with ready access to a HCP review of clinical status and support to intervene as required) demonstrated a trend towards increased time free from hospitalisation and use of other health services [40, 42, 56, 61, 67]. Models that included regular telephone support from a HCP were associated with increased self-efficacy and fewer emergency department visits, but a lack of significant impact on hospitalisation or length of stay [40, 51, 56, 71].

These variable findings can be attributed to several factors, including different study design and heterogeneity between the models of telemedicine as well as the "usual care" applied in the studies, as illustrated in table 3 [30, 33, 35, 37–48, 62, 70, 71]. Added to this is the variable frequency of telemonitoring, the different combinations of monitored clinical parameters and the differing study durations (2–19 months) [30, 33, 34, 37–48, 70, 71]. While the studies were small and heterogeneous, there are encouraging findings that telemedicine may offer clinical benefits in a selected population with COPD [21, 49, 50]. Further clarity of the effects of telemedicine is required on the following clinical outcomes: number of visits to the emergency department, number of primary care visits, number of home care or specialist visits, quality of life and mortality.

In one of the few long-term studies, 256 patients were randomised to telemonitoring or usual care over 12 months [36]. Both groups were provided with the same usual clinical care, consisting of self-management of an AECOPD, a written management plan and an emergency supply of antibiotics and steroids. The intervention group recorded and transmitted clinical parameters measured daily. No between-group differences in the time to first exacerbation, number of admissions or HRQoL were evident [36], although a slightly higher number of exacerbations was reported in the telemonitoring group.

Table 3. Studies of telemedicine in COPD

First author [ref.]	Year	Subjects n	Design	Follow-up	Description of telemedicine	Description of comparator	Outcome
Mair [57]	1999	6	Pre–post study	NR	Transmission of symptoms, S_{pO_2}, spirometry, temperature, HR and BP to HCP *via* interactive video phone.	No comparator.	NR
Bourbeau [56]	2003	191	RCT	12 months	Weekly telephone calls for self-management education for 8 weeks, followed by monthly calls for 12 months. HCP available for advice *via* telephone.	Usual care: ordinary care.	Fewer hospitalisations for exacerbations with telemedicine. Reduced ED and unscheduled physician visits. Improved HRQoL with telemedicine.
Maiolo [48]	2003	30	Pre–post study	12 months	Nocturnal S_{pO_2} forwarded by telephone to central storage. Scheduled calls by GP after analysing S_{pO_2} results.	Usual care: not provided.	Reduced number of admissions and exacerbations with telemedicine.
Vontetsianos [71]	2005	18	Pre–post study	Pre: 12 months; post: 9 months	Initial phase: patients created an electronic health record for evaluation and self-management identification of AECOPD. Chronic phase: nurse home visit to monitor vital signs and treatment compliance, and to transmit data to the hospital. Nurse communicated to PR team.	Usual care in previous year.	Fewer hospitalisations and ED visits, and reduced use of health services with telemedicine. Increased HRQoL, patient knowledge and satisfaction.
Finkelstein [66]	2006	25	RCT	6 months	Group 1: patients received two video conference visits per week with a HCP. Group 2: patients received two video conference teleconsultations per week with a HCP. Transmission of spirometry, S_{pO_2} and BP readings, and electronic diary of reported measurements and symptoms.	Usual care: standard home healthcare.	Increased activities of daily living in both telemedicine groups compared with usual care. No difference in mortality and morbidity.

Continued

Table 3. Continued

First author [ref.]	Year	Subjects n	Design	Follow-up	Description of telemedicine	Description of comparator	Outcome
Pare [40]	2006	29	Quasi-experimental	6 months	Patients provide PEFR, symptoms and medications daily *via* webphone. Reviewed daily by nurse. Both patient and nurse alerted to readings outside pre-established limits.	Usual care: traditional system of in-home visits.	Fewer hospitalisations and home visits with telemedicine.
Dang [41]	2006	17	Pre–post study	6 months	Automated system logged patient's self-reported symptoms and provided illness education. Referral alerts generated if patient's status changed.	Usual care in previous 6 months.	No difference in number of hospital bed days between groups.
de Toledo [67]	2006	157	Quasi-experimental	12 months	HCP access to electronic patient record with video conferencing teleconsultation. Patients followed-up with home visit or were able to contact the HCP team if required.	No comparator.	Fewer readmissions with telemedicine.
Whitten [11]	2007	$161^{\#}$	Quasi-experimental	11 weeks	Combination of face-to-face visits and video conference teleconsultation with a HCP weekly, with monitoring of vital signs.	Face-to-face visits with HCP.	Patients perceived video conference teleconsultation comparable to face-to-face consultation.
Trappenburg [42]	2008	165	Prospective	6 months	Usual care plus telemedicine. Daily questions on symptoms, medication compliance and knowledge. Telephone line to data centre, and automatically categorised and prioritised. Respiratory nurses reviewed patient answers and contacted the patient if status changed. The pulmonary physician or clinic were notified if required.	Usual care: usual access to healthcare providers.	Fewer hospital admissions and exacerbations with telemedicine. No difference in HRQoL.

Continued

Table 3. Continued

First author [ref.]	Year	Subjects n	Design	Follow-up	Description of telemedicine	Description of comparator	Outcome
Koff [39]	2009	40	RCT	3 months	Patients transmitted symptoms, S_{pO_2} and spirometry information to central system. Daily completion of illness education and disease management modules. Contact with a HCP *via* telephone.	Usual care: usual access to healthcare providers.	Increased HRQoL. Proactive identification of exacerbations leading to early treatment, fewer ED visits and reduced hospital admissions with telemedicine.
Vitacca [61]	2009	101	RCT	12 months	Transmission of S_{pO_2} readings by telephone to receiving station. Reviewed by a HCP daily with teleconsultation provided if required. Unscheduled calls transferred to a respiratory specialist for teleconsultation.	Usual care: standard medical follow-up.	Reduced hospitalisation, urgent GP calls and acute exacerbations with telemedicine.
Sund [47]	2009	18	Pre–post study	6 months	Mobile phone with touch-screen. Symptom and spirometry data entered. Telephone follow-up by a HCP in the event of deterioration.	Usual care: not provided.	Reduced hospitalisation rate compared with previous year, improved PFTs with telemedicine.
Lewis [30]	2010	40	RCT	6 months	Twice-daily transmission of symptoms, temperature, HR and S_{pO_2}. In the event of an alert, a HCP contacted the patient. The patient was encouraged to contact primary care on an emergency doctor if urgent treatment was required.	Usual care: standard care.	Reduced number of primary care visits with telemedicine. No difference in ED visits, hospitalisation, length of hospital stay or contact with specialist.
Sicotte [46]	2011	26	Quasi-experimental	146 days	Webphone with touch-screen monitoring. Reviewed by a HCP who initiated alerts and support by telephone.	Usual care: usual home care.	Patients satisfied with telemedicine.
Steventon [60]	2012	3230¶	RCT	12 months	Daily transmission of S_{pO_2}, HR and symptoms with education provided to a HCP. HCP reviewed data and instituted action if required.	Usual care: conventional care (range of services depending on site).	Reduced mortality rate with telemedicine. Fewer hospital admissions and ED visits with telemedicine.

Continued

Table 3. Continued

First author [ref.]	Year	Subjects n	Design	Follow-up	Description of telemedicine	Description of comparator	Outcome
Antoniades [43]	2012	44	RCT	12 months	Daily transmission of spirometry, weight, temperature, BP, S_{pO_2}, ECG, sputum, symptoms and medication usage. Data were reviewed 5 days weekly by a HCP to detect clinical deterioration and the need for intervention.	Usual care: clinical management as per guidelines, includes outreach nursing, written action plan and availability of PR.	No difference in hospital admissions per year, length of hospital stay per year, total admissions or HRQoL.
Chau [38]	2012	40	RCT	2 months	Transmission of S_{pO_2}, HR and respiratory rate three times a day to an online platform, reviewed by a HCP. Community nurse provided home visits with education on self-care strategies, lifestyle and exercise.	Usual care: home visits with education on self-care strategies, lifestyle and exercise.	No difference in HRQoL, number of ED visits, PFTs or hospital readmissions.
Dinesen [62]	2012	111	RCT	4 months	Telemonitoring of weight, BP, S_{pO_2}, spirometry and step counter. Provision of in-home exercises. Reviewed by a HCP who monitored progress and training, and provided advice to the patient.	Usual care: in-home exercises.	Reduced hospital admission rate with telemedicine. Trend towards longer time to admission with telemedicine.
Ure [35]	2012	20	Pre–post study	2 months	Touch-screen computer. Bluetooth S_{pO_2} and spirometer. Review by a HCP.	Usual care: not provided.	Improved access to healthcare with telemedicine.
Gellis [70]	2012	26	RCT	12 months	Daily telephone transmission of weight, BP, HR, S_{pO_2} and temperature. The HCP performed triage, provided education and made a home visit.	Usual care: HCP home visits.	Reduced ED visits, improved general health, improved social function and reduced depression with telemedicine.
Jodar-Sanchez [45]	2013	45	RCT	4 months	Weekday measurement of vital signs *via* telephone. Reviewed by a HCP. In the event of an alert, the HCP contacted the patient for more information and contacted the case manager who initiated a clinical response.	Usual care: conventional medical care.	Improvement in HRQoL with both groups. No difference in ED visits or hospitalisation.

Continued

Table 3. Continued

First author [ref.]	Year	Subjects n	Design	Follow-up	Description of telemedicine	Description of comparator	Outcome
Pinnock [36]	2013	256	RCT	12 months	In addition to standard clinical care, daily transmission of S_{pO_2} and symptoms (changes in dyspnoea, sputum quantity or purulence, cough, wheeze, presence of fever) to a HCP. HCP contacted the patient (*via* telephone or video conferencing) if clinical deterioration was detected, with further clinical assessment (home visit, immediate admission and prescription of rescue treatment) if required.	Usual care: standard clinical care.	No difference in hospital admissions, hospital length of stay or HRQoL.
De San Miguel [44]	2013	80	RCT	6 months	Daily transmission of BP, HR, S_{pO_2}, weight, temperature and general health. Reviewed by a HCP who acted on alerts. Telephone follow-up by a HCP. Educational booklet on COPD provided.	Usual care: educational booklet on COPD.	Fewer ED visits, fewer hospital admissions and reduced length of stay with telemedicine.
Pedone [37]	2013	99	RCT	9 months	Transmission five times per day of S_{pO_2}, HR, respiratory rate, physical activity and temperature. Review of data daily by physician. Telephone follow-up in the event of deterioration.	Usual care: standard care.	Reduced incidence of exacerbations and hospitalisation with telemedicine.
Segrelles Calvo [33]	2014	60	RCT	7 months	Daily transmission of BP, S_{pO_2}, HR and PEFR three times a week. Reviewed by a HCP who initiated alerts. Phone advice to commence treatment. Home visit as necessary.	Usual care: conventional care.	Fewer ED visits and hospitalisations, reduced length of stay, increased time to first exacerbation and reduced need for mechanical ventilation with telemedicine.

Continued

Table 3. Continued

First author [ref.]	Year	Subjects n	Design	Follow-up	Description of telemedicine	Description of comparator	Outcome
McDowell [51]	2015	110	RCT	5 months	Home-based follow-up and monitoring in addition to daily monitoring and transmission of BP, HR, S_{pO_2} and symptoms (difficulty breathing, cough, sputum, tiredness). The HCP reviewed data and instituted action if required.	Usual care: home-based follow-up and monitoring by physiotherapist and nursing with focus on education and self-management.	No difference in ED visits, hospital admission or exacerbations. Improved HRQoL and increased contact with the community respiratory team with telemedicine.
Au [59]	2015	1238	Quasi-experimental	3 years	Health Buddy Program (Bosch Healthcare, Pittsburg, PA, USA) recorded symptoms and medication use, and monitored S_{pO_2} and HR; this information was sent to a HCP. Patient advised to contact a HCP with specific alerts. HCP reviewed data and instituted action if required.	Usual care: standard care.	Fewer hospital admissions for COPD and reduced exacerbations with telemedicine. No difference in number of ED visits.

#: subjects included were diagnosed with COPD or heart failure; ¶: subjects included were diagnosed with COPD, heart failure or diabetes. NR: not reported; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; HR: heart rate; BP: blood pressure; HCP: healthcare practitioner; RCT: randomised controlled trial; ED: emergency department; HRQoL: health-related quality of life; PEFR: peak expiratory flow rate; GP: general practitioner; PFTs: pulmonary function tests.

Another study explored the role of telemonitoring 7 days a week, with out-of-hours physicians available for patient management [51]. While hospitalisation rates did not differ between groups, there was a significant improvement in HRQoL, with less anxiety noted among the telemonitoring group [51]. A key factor in this study was the frequency of follow-up telephone calls from HCPs and contact with the community team [51], which may influence the success of telemonitoring.

The effectiveness of an intervention that includes telemonitoring is dependent upon patient adherence, reported as ranging 40– 98% [38, 43, 47]. It has been suggested that overly frequent monitoring may reduce adherence [55]. Adherence was unaffected by the severity or complexity in clinical presentation, with a compliance of 71% in those with severe COPD prescribed long-term oxygen therapy [45] and high adherence rates in those with multiple comorbidities [33]. Strategies to optimise adherence need to be considered when implementing a telemonitoring model.

A determinant of whether telemedicine will reduce the rate of AECOPD and hospitalisation is the timely recognition of clinical deterioration. While various algorithms have been derived [73], further clarity on which parameters best detect an AECOPD is required [31, 36, 74]. The lack of clear patterns of normality and what precisely defines an exacerbation are also limiting factors [52, 75]. For these reasons, it is recommended that the selection of suitable patients for telemonitoring incorporates a comprehensive assessment by a HCP of an individual patient's clinical trends to facilitate effective monitoring.

Effects of telemedicine in the management of AECOPD

AECOPD are a major cause of hospital admissions and death [76], accounting for up to 50% of healthcare costs [77]. Prompt intervention is critical to preventing hospital admissions and reducing hospital stay [78]. Telemedical technology may be used to support an admission for an AECOPD in a patient's home rather than in hospital [79]. A recent Danish randomised controlled trial recruited patients diagnosed with an AECOPD within an emergency department to a virtual hospital [80]. Those in the intervention group received training in video conferencing and monitoring within the emergency department, with telemedicine then activated within the patient's home and maintained for 1 week. This was supported by 24-h online access to the hospital HCP as well as the provision of oxygen and medical therapy, and the surveillance of vital parameters using telemonitoring equipment at home. Control subjects received usual protocol-directed hospital care. This non-inferiority trial noted similar improvement in HRQoL and daily activities at 6 and 12 weeks post-discharge from acute care in both groups [81]. These preliminary findings suggest a potential role for telemedicine in AECOPD management [81].

Other studies have explored the impact of teaching patient empowerment, self-care and medication use *via* telemedicine following hospitalisation for an AECOPD [82]. While there was no significant reduction in hospital admissions compared with the previous 12 months, selected patients (48%) indicated a preference for comprehensive telemedicine rather than telephone follow-up during this recovery phase [82]. Similar Danish studies compared usual care to daily video consultations between a HCP and patients recovering from an AECOPD over 6 weeks [83, 84]. At 4 weeks follow-up, fewer patients undergoing telemedicine were readmitted, with a longer time to readmission, although these findings

Table 4. Patient-perceived benefits of virtual admission during AECOPD

Sense of dependency on health professionals, relatives and medical equipment
Security based on presence of others
Confidence to approach HCP sooner to determine the need for a hospital admission
Feeling less constrained compared to hospital setting
Free from disturbances from other patients
Comfort from being in their usual surroundings
Facilitates early return to daily life and activities of daily living
Expectations of maintaining control of their condition by using the medical equipment
Interaction between patient and HCP is on patient's terms
Gain information about their condition by using monitoring devices

HCP: healthcare practitioner. Data from [79].

were not statistically significant [83]. Studies of a longer duration are necessary to further define this approach.

While virtual admission aims to improve patient autonomy, there is some concern that the telemonitoring and communication required during an AECOPD may cause additional stress. However, patients identified several benefits of virtual admission (table 4) [79]. Although self-efficacy did not improve [85], which questions whether an AECOPD is the optimal time to address self-efficacy, there was no evidence of a negative impact on cognitive function post-discharge [86]. Introducing telemedicine at the time of an AECOPD is feasible; its clinical benefits require further clarification.

Effects of telehealth in patients with stable COPD

A systematic review of nine studies summarised the impact of telehealth, which included reinforcement of exercise or activity, web-based education and support for self-management strategies compared with usual care [87]. While improvement in physical activity by 64.7 min (95% CI 54.4–74.9 min) was achieved with a mix of strategies, there was no difference in walking distance or dyspnoea intensity [87]. This suggests that to improve physical activity using telehealth technology, the support of a HCP for regular feedback is necessary [24, 88].

A more recent study examined the effects of telehealth on behaviour modification [22]. Patients focussed on a specific aspect of behaviour (smoking cessation, medication adherence or physical activity) for 3 months, with suggestions to facilitate change provided on a regular basis [22]. There were small improvements in HRQoL and an increase in the number of days in which patients were physically active, but there was no improvement in smoking cessation. If telehealth is to provide a role in behaviour modification, the programme components, mode of delivery and duration of intervention are yet to be established [89].

Cost-effectiveness of telemedicine

A systematic review of six studies suggested the potential for cost savings with telemedicine in COPD [90]. However, when telemedicine was added or compared with usual care, the findings were inconsistent, ranging from no benefit [62] to some reduction [40, 44, 61, 64]. In a cost utility analysis of patients who received telemonitoring compared with usual care, no benefit in QALYs was evident [45]. A telemonitoring programme applied over a longer duration (6 months) was associated with a total cost of £2039, with an incremental cost-effectiveness ratio of £203 900 [51]. With an incremental cost-effectiveness ratio threshold of <£20 000 considered cost-effective [91], this programme was not economically beneficial [51]. A more comprehensive study of cost utility, which included costings of equipment and infrastructure, found higher intervention costs with telemonitoring compared with usual care, and no difference in QALYs at 12 months [92]. Consistent with these findings was the recent observation that while telemonitoring was not significantly more costly than usual care, it was not cost-effective with respect to QALYs [93].

Long-term assessment of cost-effectiveness should include shared resources, marginal costs and salaries [94]. With the development of telemedicine partially driven by economic demand, it is thought that telemedicine should be more cost-effective than traditional care [11]. Considering the investment in equipment, infrastructure, personnel and patient training, and in time instituting the service, determining the cost-effectiveness of telemedicine is critical. As the greatest cost is associated with hospitalisations [45], it is hoped that with earlier diagnosis and management of an AECOPD, these models of care will become cost-effective. This information is necessary, as is the need to establish the effect on the number of hospital or community healthcare visits and on the medication prescribed, in order to clarify the direct and indirect cost of this intervention and its cost-effectiveness potential.

Despite the absence of conclusive evidence supporting the benefits of telemedicine, the concept and its potential to improve care are appealing. However, identifying the patients most likely to benefit from telemedicine and establishing the most effective monitoring and consultation protocols remain a challenge.

Attitudes of patients and HCPs to telemedicine

Patient opinions

Patient and caregiver perspectives of telemedicine are important [32], and patient opinions relating to the key themes of telemedicine are outlined in table 5. Irrespective of disease severity, patients generally expressed considerable positivity and satisfaction, citing earlier recognition of AECOPD, greater access to healthcare services, reassurance and a sense of security as important benefits [35, 44, 45, 55, 69, 95]. Patients reported greater confidence in their ability to recognise trends in symptoms [35, 53]. However, those who are constantly symptomatic require additional support in establishing their symptom baseline [35].

The enhanced communication and dialogue between the patient and the HCP was considered beneficial by most patients [11, 53, 55, 96]. Most individuals receiving telemedicine expressed a desire to extend the application beyond a trial period [38]. There is particular appeal for patients in rural or remote communities, for whom the increased access to healthcare services and elimination of extensive travel was particularly beneficial [10, 35, 97]. For those engaged in teleconsultation *via* video conferencing with a HCP on a regular basis, patients indicated significant satisfaction that was comparable to face-to-face consultations and no concerns relating to efficiency [11]. The lack of physical presence did

Table 5. Patient perspectives of telemedicine

Positivity and satisfaction with earlier recognition of AECOPD and access to services

"Before…I never know whether I needed them, you know and it was get up to A&E and admitted to hospital…Well now I've got that telehealth, I can get in touch with them and they'll check the readings…They will come out if you ask them to…no problem." [55]

"Well you know yourself within those 3 or 4 days if an exacerbation takes hold of you it does take a hell of a lot of moving…but with that thing they're on the phone and they're within a couple of days, you've got all your results." [53]

"My weekly contact with the healthcare professionals helped me to gain new knowledge about how to handle my own disease in different situations of everyday life." [95]

"You'd think you would find it easy to tells when you're ill but it's only afterwards that you know you are not well. But this technology is really brilliant." [35]

"I think the problem is that somebody who's close to you, you know, I'll say 'I don't think your breathing's very good, I think you ought to ring the doctor or I'll ring the doctor', but I say "No, I'm alright", but if that telehealth tells us to ring, we'll ring." [53]

"I felt like I was being monitored, I felt like a connection, to be honest…to the team." [10]

Increased patient confidence

"It's made me more confident in myself because I know what's happening. If I didn't have that telehealth, I wouldn't know how low I was, I'd just carry on with a normal day, wouldn't I? Now you've got that, it puts you aware of what's happening." [53]

"I'm quite chuffed [pleased] with it, being able to understand what it's all about, blood pressure, S_{pO_2}, temperature and weight, I've been more relaxed and content." [35]

"It has stopped me pressing the panic button so often." [53]

Reduced need to travel for medical care

"I will get that secondary care, but don't have these horrendous journeys to get there and then be admitted overnight for no reason at all other than that I had to travel." [53]

Peace of mind

"It settles your mind more than anything…peace of mind…I've got to be honest with you on that. It does save me a lot of aggravation" [53]

A&E: accident and emergency; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry.

not present a fundamental obstacle to undertaking a thorough consultation between the patient and the HCP.

Given the age and frailty of some individuals with COPD [98], it is important to employ user-friendly technology. When trained for clinical studies, patients generally reported feeling comfortable with the equipment [35, 40, 43, 44, 69, 99–101], despite their limited previous exposure to technology and some initial hesitance [11, 100]. Although equipment was usually well integrated into the home environment, technical failures were often reported by patients [35, 55]. These were frequently easily resolved so as not to disrupt the intervention.

HCP opinions

Many HCPs have expressed concern that telemedicine may increase patient dependence rather than promote self-care [46, 102]. However, others noted that this was contradicted by empowered patients taking responsibility for initiating emergency courses of treatment [11, 46]. Some HCPs reported concerns relating to the over-diagnosis of clinical decline and the initiation of unnecessary treatment [35]. An important element is continuity of care, with the same HCPs being consistently accessible for a particular patient [96]. This continuity, together with a clear set of individualised indicators of decline, is necessary to maximise the accuracy of detecting clinical deterioration [103].

From a HCP's perspective, it is important to consider how this new technology may complement existing services prior to embedding it into clinical practice [104]. Incoming data must be monitored and responded to in a timely manner [35]. HCPs recognise the need for clear delineation of the roles and responsibilities, as well as the need for excellent communication with patients' GPs and respiratory specialists [96]. Practitioners have expressed concerns relating to the time commitment for training and provision of telemedicine, which can increase the workload of HCPs [35, 44, 69, 104]. As with all new technologies, on-hand technical support will be necessary. Moreover, ensuring a good-quality digital infrastructure is essential, especially for rural or remote areas that may be disadvantaged by their lack of connectivity [10]. Each of these factors will influence the application of telemedicine to the broader community.

The application of telemedicine in other chronic conditions

Respiratory conditions

Telemedicine has been applied in respiratory conditions other than COPD, including asthma and CF [10, 16, 54, 105]. In CF, a systematic review concluded that telemedicine was feasible but there was insufficient evidence of clinical benefits [105]. In asthma, patient acceptance was high [10], with greater benefit being reported in those at a higher risk of hospital admission [106].

Telemedicine has been used for individuals with chronic respiratory failure secondary to neuromuscular disorders, who require long-term ventilation and have high healthcare needs [61, 107–109]. The difficulties in accessing healthcare for these individuals, coupled with a high carer burden and the need for ongoing dynamic decision-making, provides a strong rationale for telemedicine. The provision of telemonitoring and telephone or video conferencing to facilitate adjustments to ventilator settings and the management of clinical status change *via* scheduled or unscheduled interaction is not only feasible but is associated with increased patient and carer satisfaction, as well as a reduction in medical practitioner workload [107–109]. These positive findings suggest that even individuals with respiratory conditions associated with high healthcare needs can significantly benefit from telemedicine.

Non-respiratory conditions

Telemedicine has also been applied in individuals diagnosed with congestive heart failure and diabetes [110–112]. In congestive heart failure, there is evidence of a significant reduction in all-cause mortality, heart failure-related hospitalisation and resource utilisation, as well as improvement in HRQoL [110, 111]. In diabetes, various telemedicine strategies have been associated with a significant reduction in HbA1c, in comparison with usual care [112]. The clinical findings of telemedicine in these two chronic conditions, both of which are comorbidities of COPD [113, 114], suggest that for selected patients with COPD who present with multimorbidities, telemedicine is a possible management option. Telemedicine, including monitoring and education, has been previously applied in individuals diagnosed with COPD, heart failure or diabetes, with the overall telemedicine approach individualised for the patient [60]. The success of this approach in reducing mortality and lowering emergency admission rates across these chronic conditions suggests that applying a tailored package of telemedicine based on an individual's primary and comorbid conditions may be possible. Further study is required to explore this concept.

Standards of practice and precautions of telemedicine

There are guidelines for standards of practice in telemedicine to ensure safe and prompt patient management. Key components of these standards are a framework for contact with users and carers, staff management, personal information management, interpretation of and response to information, network communications, hardware and technological considerations, and ethical issues [115, 116]. Critical points and themes within these standards are outlined in table 6 and it is important that telemedicine applications in COPD adhere to these standards.

The transfer of medical information introduces issues of privacy and confidentiality. Electronic communication of personal information is regulated by national legislation [117, 118]. All health-related information concerning an identifiable person is considered sensitive [119] and only HCPs with a treatment relationship with the patient should have access to that individual's health information [34]. Possible risks and threats to security related to telemedicine include unauthorised persons being present during the teleconsultation or review of the collated information, inaccurate or lost data entry or inability to transfer data (power failure, data corruption) [34]. While not widely identified as a patient concern [11], proactive and preventative strategies to ensure patient security and privacy are important.

Telerehabilitation for patients with COPD

The most recent addition to telemedicine is telerehabilitation, a way of providing supervised PR at a remote location, such as in the home or at a satellite class at a community centre [120]. PR is an integral part of the long-term management of COPD. It consists of exercise training, patient education and psychosocial support [121]. Although there is strong evidence that PR will improve exercise tolerance and quality of life, while reducing symptoms and optimising participation in activities [121, 122], limited access and poor adherence result in <5% of eligible people with COPD receiving PR each year [123–125]. Common barriers include a lack of rehabilitation programmes, poor patient access to existing programmes due to lack of transport [123, 126] and inconvenience of hospital attendance [127].

Distance PR involves a variety of technologies, including telephone and video conferencing, and complete online exercise supervision used to reinforce training [26, 128–131]. Recent studies exploring the effects of telerehabilitation in people with COPD are outlined in table 7. In a Canadian study, distance PR through community satellite centres even with limited equipment was associated with similar improvements in HRQOL, but less improvement in 12 min walking distance compared to a centrally supervised programme [130]. The potential advantages of reduced patient travel make this form of satellite PR programme an attractive option that may yield value to a larger patient capacity.

Two studies have reported initial success in providing distant supervision of cycle exercise training for 8 weeks *via* personal video conference plus patient monitoring [26, 128]. Tousignant *et al.* [128] reported three patients with COPD who experienced improvements

Table 6. Themes within standards of practice in telemedicine for COPD

Healthcare practitioner

- Adheres to standards of practice and national guidelines in the provision of telemedicine.
- Makes information about the service available to patients and carers to enable informed choices regarding their acceptance (or not) of the service and service options.
- Follows ethical and legal requirements to obtain valid informed consent, and to protect the privacy and confidentiality of patient information.
- Will have the necessary education, training/orientation, licensure and ongoing continuing education to ensure the necessary knowledge and competencies for the safe provision of quality health services.
- Healthcare practitioner's site to use appropriate technology that complies with legal requirements regarding privacy and security, and accreditation standards where required.
- Familiar with the use of devices and software employed in delivering care over distances, and ensures proper functioning, confidentiality, security parameters and infection control policies for telemedicine equipment.
- Provides their identity, qualifications and license information to the patient, with confirmation of the patient's identity at each consultation.
- Aware of patient's geographic location.
- Explains the appropriateness and limitations of technology-based patient consultation and considers whether a physical examination is necessary.
- Where involved in remote monitoring, will ensure that timely action is taken where there is a known or indicated change in health, well-being and/or personal circumstances of the patient or carer(s).
- Maintains comprehensive and up-to-date medical records in relation to service provision.
- Communicates with referring and other treating physicians, and provides follow-up and care as medically appropriate.
- Exercises caution when providing prescriptions or other treatment recommendations to patients they have not personally examined.
- Familiar with local in-person health resources and exercises clinical judgment to make a referral for additional health services when appropriate.
- Culturally competent in delivering services to the populations that they serve.

Patient

- Uses appropriate technology that complies with legal requirements regarding privacy and security and accreditation standards where required.
- Receives adequate training in the use of devices, equipment and software to ensure the safe and effective operation of the telemedicine service.
- Aware of the healthcare practitioner's physical location (*e.g.* clinic, town, state).

Institutions responsible for service provision and delivery

- Ensures that only authorised staff are able to input, amend or access personal information regarding patients and carers, and their service usage.
- After service cessation, keeps the personal information of patients and carers secure pending its transfer, deletion and/or anonymisation.
- Engages a sufficient range and number of staff commensurate with safe and effective and sustained operation of the service.
- Provides staff with (or supports them in accessing) training.
- Has policies, where included as part of the contracted service, for teleconsultations (*via* video) to users and carers.
- Provides guidance and, where appropriate, training to service users and carers.
- Provides service users and carers with an easy means of reporting faults or failures of the technologies/equipment.
- Monitors the communications networks used to ensure that they are operational and that faults are speedily identified and remedied.
- Operates technologies/equipment (including operational software and, where applicable, apps) that are "fit for purpose" and conform to relevant regulatory standards.
- Makes provision for the protection, safe operation (including maintenance, servicing and repair) and storage of technologies/equipment; and of the related physical and communications infrastructure.
- Ensures the provision of a readily available technical helpline to trouble-shoot issues that may arise for the patient regarding equipment operation and processes.

Data from [115, 116].

Table 7. Studies of telerehabilitation in patients with COPD

Study	Year	Subjects n	Disease severity	Intervention	Outcomes
Strickland [130]	2011	Standard PR: 262 Satellite PR: 147	Standard PR: FEV_1 49% pred Satellite PR: FEV_1 48% pred	Standard PR: twice weekly for 8 weeks. Supervised by respiratory therapist with 2 h of aerobic (walking, cycling arm ergometry) and resistance (hand weights, elastic tubes) training, flexibility and breathing retraining. Education modules for self-management. Satellite PR: local health facility twice weekly for 8 weeks (2–6 patients per site). Same protocol as above. Respiratory therapist trained and guided by standard PR respiratory therapist. Education modules *via* video conferencing, facilitated by standard-PR respiratory therapist.	Similar rates of adherence and increased HRQoL (SGRQ); both increased 12MWD, greater in standard PR (690 m *versus* 631 m).
Tousignant [128]	2012	3	FEV_1 ranged 42–55% pred	Telerehabilitation: stationary cycling for 10–45 min for 8 weeks (gradually reducing supervision from three times per week to unsupervised (weeks 6–8)). Supervision *via* personal video conferencing. Monitored S_{pO_2}, HR, dyspnoea and fatigue.	Improvement (>54 m) in 6MWD in two participants. Trends towards improvement in HRQoL.
Zanaboni [27]	2013	10	FEV_1 39% pred	Home-based telerehabilitation: remote supervision by physiotherapist weekly, individually or with other patients. Exercise three times per week, endurance and resistance training. Tablet computer with built-in web camera for personal video conferencing. Monitored S_{pO_2}, HR, dyspnoea, cough and sputum.	Nonsignificant reduction in hospital visits and length of stay over 6 months.

Continued

Table 7. Continued

Study	Year	Subjects n	Disease severity	Intervention	Outcomes
Holland [26]	2013	8	FEV_1 66% pred	Remote home supervision by physiotherapist. Cycle ergometer twice per week for 8 weeks. Physiotherapist supervised two patients at once in real-time. Exercise up to 30 min, then increased intensity. Self-management: healthy living with COPD. Tablet with personal video conferencing, monitored S_{pO_2}, HR, dyspnoea and fatigue.	Completion of 76% of sessions. Increase in 6MWD (27 m) and decrease in dyspnoea and fatigue. No change in emotional function or mastery. Usability score of 94% for university data network and 59% for hospital data network.
Paneroni [129]	2014	Telemedicine PR: 18 Standard PR: 18	Telemedicine PR: FEV_1 47% pred Standard PR: FEV_1 43% pred	Telemedicine PR: 28 sessions over 40 days, 40 min cycle ergometry, 40 min resistance training, 20 min stretching. Exercise provided by interactive tablet, supervised by physiotherapist through personal video conferencing or unsupervised. Prescription adjusted every 2 days by physiotherapist. Education by telephone or personal video conferencing as needed. Monitoring S_{pO_2}, BP, dyspnoea and fatigue. Standard PR: Three sessions per week, maximum of 6 days per week, protocol as above. Face-to-face supervision and education by physiotherapist. Monitoring as above.	Telemedicine PR patients: 88% said project met clinical expectations, 67% rated as very good, 17% rated as good. Increase between groups in steps per day (3412 *versus* 1863; p=0.0002). Both showed increases in 6MWD, MRC dyspnoea score and HRQoL (SGRQ).

% pred: % predicted; HRQoL: health-related quality of life; SGRQ: St George's Respiratory Questionnaire; 12MWD: 12-min walk distance; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; HR: heart rate; BP: blood pressure; MRC: medical research council.

in walking distance and trends towards improved HRQoL. Similar improvements were noted in the pilot study by Holland *et al.* [26], in which the HCP monitored two patients simultaneously, enabling some patient interaction and the possibility of patient support, even in the absence of group interaction. Having even a single training partner as part of telerehabilitation may reduce the isolation of individuals with COPD who are housebound but are participating in exercise training. As with other applications of telemedicine, technical issues required ongoing support [26].

In a modified version of telerehabilitation, home exercises were demonstrated *via* interactive television, with supervision subsequently provided *via* videoconferencing for 28 sessions over 40 days [129]. Remote monitoring of symptoms and arterial oxygen saturation measured by pulse oximetry was used by the supervising therapist to guide exercise progression. When compared to hospital-based outpatient PR of the same duration [129], this model of telerehabilitation was found to be safe and achieved equivalent benefits in walking capacity and HRQoL [129]. Despite the differences between these innovative modalities of telerehabilitation, they illustrate the safety and feasibility of this option, and possible short-term clinical benefits.

One study examined the effects of long-term maintenance exercise training at home, with the programme supported by videoconferencing and remote monitoring of symptoms and oxygen saturation in 10 patients who completed a formal PR programme [27]. Active participation in exercise and training was still evident after 2 years. This suggests that enabling continual dialogue of motivation and encouragement between a physiotherapist and patient exercising at home may be a key factor in ensuring longevity in training [27]. The current mix of short- and long-term studies provides a promising direction for future research that explores the effects of telerehabilitation models in larger trials.

Future directions of telemedicine

For a chronic condition such as COPD, there is a continual need for active and integrated support, to engage patients in their own healthcare management. In addition to team member collaboration, future directions for telemedicine may involve synchronisation of an overall care plan for patient management. Telemedicine may also promote social support for isolated individuals with COPD who live alone; the extent of this requires further study [132]. Although monitoring of an individual by a HCP may provide reassurance to family members, telemedicine technology used may also enable them to monitor their relatives remotely [133]. With advances in technology, monitoring is likely to become less onerous for patients. The constant emergence of mobile technologies, including electronic applications and other digital tools that are increasingly used by patients, is likely to drive expectations that healthcare service delivery will accommodate these devices and tools into their diagnostic and treatment protocols.

Conclusion

Telemedicine has the potential to enhance healthcare delivery to patients with COPD, through education and regular monitoring to identify acute exacerbations. However, current models are limited by the heterogeneity of their interventions. In many patients, acceptance and satisfaction is high. But the complexity of the equipment, the demands of regular monitoring and the need for technical support and infrastructure underline the importance of selection of the patients and the HCPs most likely to engage meaningfully in telemedicine. The most optimal and cost-effective method has not been identified. When introducing telemedicine, it is important to use it to complement healthcare services and target those who may be in greatest need.

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The challenge of palliative care

Laura-Jane Smith[1] and Jennifer K. Quint[2]

Case history: A 75-year-old woman with an FEV_1 of <0.4 L is admitted to hospital for the second time in 6 months with an exacerbation of COPD. She is an ex-smoker, and takes inhaled long-acting antimuscarinics, long-acting β-agonists and ICSs regularly. She does not meet criteria for long-term home oxygen. Prior to admission, she walked short distances indoors, limited by dyspnoea, and used a mobility scooter to get to the local shop. Her functional abilities have declined over the last year, and she has lost 10% body weight such that her BMI is now 20 $kg \cdot m^{-2}$. Following acute treatment with controlled oxygen, oral steroids and antibiotics, and a prolonged hospital stay, she remains breathless at rest with severe fatigue and anxiety. A trial of low-dose opioids has been suggested but she is reluctant to start this treatment due to fears of dependence and drowsiness. A case-conference is planned to address her ongoing needs and preferences for future care. Her daughter has asked about her likely prognosis, and how her symptoms and quality of life can be improved.

Chapter summary: As the prevalence of COPD increases globally, there are a growing number of patients living with disabling symptoms and impaired quality of life, before a premature death. Such patients may benefit from a more holistic approach to their condition, including better symptom control and earlier referral to palliative care. Barriers preventing COPD patients accessing palliative care include prognostic uncertainty and a limited evidence base for both pharmacological and non-pharmacological interventions. Interventions that are evidence-based are not widely available to patients with COPD, partly due to models of care that are based on acute crises rather than longer-term support. Further research into treatment for breathlessness, anxiety, panic disorder, fatigue and pain in COPD is needed, as well as evaluation and optimisation of new models of care. Respiratory and palliative care specialists must work in parallel to better support patients and their carers.

The natural history of COPD follows the organ failure trajectory [1], with a gradual decline in function punctuated by acute exacerbations, making outcome and prognostic assessment challenging in individual patients. Symptom burden and functional impairment are comparable to advanced cancer [2, 3], with impaired health-related quality of life despite maximal treatment [4, 5]. Patients with advanced COPD have similar treatment preferences to patients with lung cancer [6] but are more likely to undergo invasive interventions near the end of life [6–8] and less likely to complete advanced care planning or access specialist palliative care services [3, 9, 10].

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There is often a lack of information from healthcare professionals regarding prognosis and social support. Informal carers take on a significant burden of emotional and practical support [11, 12], and have high rates of post-bereavement depression. All of these factors suggest that a palliative care approach would be beneficial for patients with advanced COPD; indeed, both national and international guidelines recommend such an approach [13–16]. However, patients with COPD fail to reliably access a palliative care approach [5, 17]. There are specific challenges around prognostic uncertainty: patient and physician knowledge and expectations, the interplay between generalist and specialist palliative care, the evidence for interventions, and models of care that require exploration. At a time of increased political commitment to high-quality palliative care regardless of diagnosis [18–20], further investment in research is needed in this field.

The definition of palliative care

Most people think about cancer when they think about palliative care, but there is increasing recognition that patients with non-malignant chronic disease have needs that benefit from a palliative care approach, and that such care can be delivered alongside other life-prolonging therapies. Inherent in the World Health Organization (WHO) definition of palliative care is the fact that palliative care is an approach to care, and is not defined by the individual components of this care, the location in which care is delivered, or the healthcare professionals who are involved [21]. A challenge is to differentiate end-of-life care, focussed on the last weeks and days of life, from palliative care, a much longer-term approach to care that can begin at any point in the trajectory of a life-limiting illness and can coexist with other “active” or disease-orientated treatments (figure 1). It is particularly important to make a distinction between these two terms in the context of COPD, as the time-frame over which a patient may benefit from a palliative care approach may be several years.

Respiratory specialist teams may lack experience in attending to the psychological, religious and spiritual needs of their patients, leading to patients with COPD rating communication about psychological and spiritual aspects of care as poor [23]. There are known to be high rates of anxiety and depression in severe COPD, but these psychological comorbidities are still not routinely screened for, and are under-treated [5, 6, 10, 24–26]. Increasing awareness of wider aspects of care within the respiratory community, accessing education and training on how to assess these needs, and constructing models of close working with specialist palliative care teams to offer appropriate support, are essential in moving forward to provide high-quality palliative care for patients with COPD.

The initiation of palliative care must not be seen as an end to treatment or as an inevitable start of the end-of-life phase. In fact, a palliative care approach can not only enhance quality of life but may extend the duration of life (figure 2) [28–30].

Prognosis and the problem of “prognostic paralysis”

Despite the high prevalence of COPD, relatively little is known about the late clinical course of the disease in comparison with malignant disease, or other life-limiting non-malignant diseases such as heart failure [9]. Although a palliative care approach should not be reserved for those in the last weeks and months of life, traditionally, prognosis has been the way patients have been identified for such care and services.

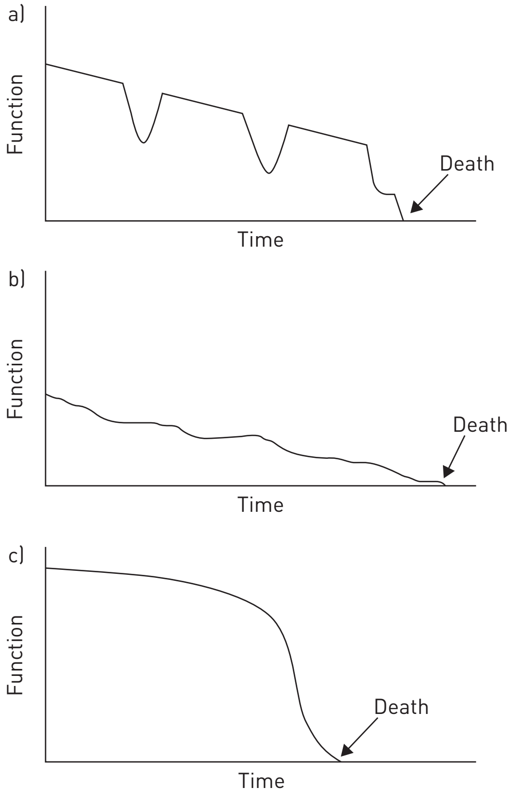

Figure 1. Disease trajectory. a) Heart failure or COPD, b) dementia or frailty, and c) cancer. Reproduced and modified from [22] with permission from the publisher.

Guidelines that advocate increased advance care planning suggest identifying patients with a likely prognosis of less than 6 months to a year in whom to start such conversations [13]. This creates a challenge in COPD since even within the group of patients classed as severe or very severe [16], it is difficult to identify those patients who are likely to die in this timeframe [31]. Alternative strategies are moving to a needs-based approach for service delivery [32], and identifying transitions in the course of the disease, as triggers to initiate advanced care planning [33]. Both of these approaches have advantages, but there remain growing calls from patients, their relatives, healthcare professionals and policy makers for better tools for prognostication [34–37].

Stewart and McMurray [38] have described "prognostic paralysis", in which clinicians faced with uncertain disease trajectories (particularly in COPD, cardiac failure and dementia) hesitate and delay considering end-of-life issues, leading to failure to offer patients a palliative care approach that could in fact enhance quality of life.

Clinicians' estimates of prognosis

It is well documented that clinicians' estimates of prognosis in malignant [39, 40] and non-malignant life-limiting disease are inaccurate [41–43], even if the clinicians are highly experienced. Most often, predictions are overly optimistic and there is vast inter-rater

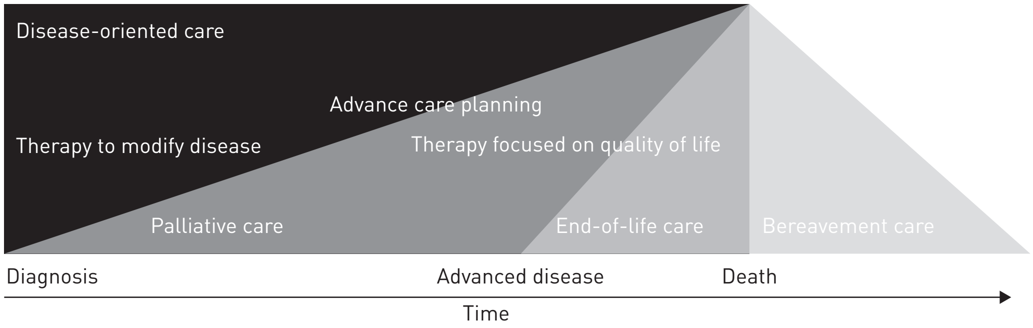

Figure 2. Diagram of components of care: life-prolonging, palliative, end-of-life. Reproduced and modified from [27] with permission from the publisher.

variability [42]. Estimates of survival vary amongst physicians in patients with COPD, perhaps partly because of differential weighting of physiological and social factors [44]. The COPD and Asthma Outcome (CAOS) study, which considered people with asthma and COPD, found that clinicians' predictions were generally pessimistic in patients being considered for admission to an intensive care unit, as compared to actual survival [45]. Clinicians seem more comfortable with, and accurate at predicting, mortality in patients with cancer compared with non-malignant disease [6]. There is therefore a need to stop relying on intuition and to develop instruments that could aid more reliable clinical predictions [34, 46].

Prognostic markers

Traditionally, prognosis has been based on age, FEV_1 % predicted, hypoxaemia or development of cor pulmonale [47]. However, within these groups, which mark out patients with "severe" disease, there is great heterogeneity; these are therefore poor prognostic markers in individual patients [48–50]. Attempts have been made to identify additional prognostic markers (table 1).

A limitation of many existing studies is that they have been conducted in specific populations [8, 43, 52–54]. The findings are therefore not applicable to the large population of patients with moderate-to-severe COPD in the community. Since we increasingly recognise that COPD is a heterogeneous group of conditions with various contributing pathophysiological mechanisms [58], it is not surprising that such studies have been unable to find reliable single generalisable prognostic markers.

Prognostic models

In recognition of the fact that individual prognostic markers are inadequate for making accurate predictions for individual patients, researchers have examined clusters of symptoms and patient characteristics, and used them to pragmatically direct the allocation of specialist services. These include: FEV_1 <30% pred; declining performance status; walk distance of only a few steps; >1 urgent hospitalisation in the last 12 months; cardiac failure or other chronic comorbid disease; older age; depression; and living alone [59]. Attempts have been made to more rigorously assess the validity of such clusters of patient characteristics by using statistical and epidemiological techniques to create models. Such models exist for populations like the hospitalised elderly [60] and the critically ill [61].

Table 1. Prognostic markers that may potentially be used

First author [ref.]	Prognostic marker	Findings
Nishimura [48]	Breathlessness	Breathlessness was a better prognostic marker than FEV_1 %
Soler-Cataluña [51]	Exacerbation frequency	Exacerbation frequency correlated with lung function decline and mortality
Knaus [43] **Connors [8]** **Almagro [52]**	Hospitalisation for exacerbation	A mortality of 13.4–34% at 6 months and 22–43% at 12 months was found post-hospitalisation
Ai-Ping [53] **Nevins [54]**	ICU admission for exacerbation	In those admitted to ICU, 8–28% died in hospital, ~39% at 6 months and ~43% at 12 months
Pinto-Plata [55]	Exercise tolerance, 6MWT	6MWT, particularly change over time, was found to independently predict prognosis in a group of 198 patients with severe COPD, after accounting for age, BMI and FEV_1 %
Coxson [56]	Biomarkers such as SP-D and sRAGE	Some biomarkers have been associated with lung function decline but as yet there are no biomarkers that provide meaningful information on rate of decline or prognosis
Connors [8]	Severity of illness, low BMI, older age, poor prior functional status, P_{aO_2}/F_{IO_2} ratio, comorbid congestive cardiac failure, low serum albumin and cor pulmonale	Multiple factors were identified as independently related to survival time in the SUPPORT study, but without clear evidence of which was most useful
Dallari [57]	RVSP, FEV_1, P_{aO_2}	Within patients on LTOT observed for 24 months, several additional factors were predictive of mortality

ICU: intensive care unit; SP-D: surfactant protein-D; sRAGE: soluble receptor for advanced glycation end product; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; SUPPORT: Surfactant, Positive Pressure, and Oxygenation Randomized Trial; RVSP: right ventricular systolic pressure; LTOT: long-term oxygen therapy.

In COPD, the most widely known and best validated model is BODE, which includes BMI, degree of obstruction of lung function (FEV_1 % pred), dyspnoea (Medical Research Council (MRC) score) and exercise tolerance (6MWT) [62]. The ADO, a modification of BODE, only uses age, dyspnoea (MRC or the St George's Respiratory Questionnaire) and lung function (FEV_1 % pred) and was constructed for use in community settings [63]. A large-scale international validation led to an update in the score to improve discrimination [64].

A number of criteria have been suggested to ensure that future prognostic models are more likely to be integrated into clinician decision-making and therefore have an impact on patient care (table 2) [65].

The analysis of data from electronic health record databases of routinely captured data offers an opportunity to create and validate models that would meet these criteria, and potentially identify patients in the last year of life [66]. Prognostic markers and combinations of such markers that warrant further investigation in this context include those in table 3.

Challenge: To identify those who will benefit from a palliative care approach.

Recommendation: To take a holistic approach and introduce palliative care to COPD management at an early stage, in parallel with disease-oriented care.

Research needs: In view of its importance to patients and relatives as well as professionals, further research is needed on prognostic markers in COPD.

Symptom burden in advanced COPD

Patients with advanced COPD have a significant symptom burden, which is at least as great as that of patients with lung cancer [3]. According to bereaved informal caregivers, patients in the last year of life experience breathlessness (94%), anorexia (67%), pain (77%), cough (59%), insomnia (65%), confusion (33%) and low mood (71%) [9]. In neither study did patients with COPD have support from a palliative care team. Other studies have found a significant symptom burden, particularly breathlessness, fatigue and limitation of daily

Table 2. Criteria to ensure prognostic models are clinically useful

Clinical credibility
- Patient data required for model easily and reliably accessible
- Avoid arbitrary thresholds for continuous variables
- Simple to calculate at point-of-care

Evidence of accuracy
- At least as accurate as clinician prediction
- Low false-negative and false-positive rate
- Error rates tested in large dataset not used to generate model

Evidence of generality
- Model testing in other populations, in time and space
- Each item of data clearly defined to ensure easy use in other settings/languages
- Prospective validation in well-defined population

Evidence of clinical effectiveness
- Measure effects on practice and outcomes of using model
- Compare to phase III study in drug trials

Table 3. Prognostic markers in COPD that warrant further investigation in risk models generated from large datasets

- FEV_1 % predicted
- Presence of specific comorbidities and/or number of comorbidities
- Breathlessness
- Functional status
- Previous episodes of noninvasive and/or invasive ventilation
- Health-related quality of life
- Quality of life
- Socioeconomic group
- Healthcare utilisation (*e.g.* number of hospital admissions in previous year, number of hospital inpatient days, contacts with community respiratory team)
- Weight loss, cachexia or BMI <21
- Exercise capacity
- Use of long-term oxygen therapy and/or home noninvasive ventilation
- Social isolation and/or marital status
- Use of long-term steroids

activities, often leading to social isolation [67, 68]. Anxiety, panic and depression are also prominent and under-treated [5, 6, 24]. Unsurprisingly, quality of life is impaired even in those with mild disease, and continues to deteriorate in those with severe disease [3, 9, 69, 70]. However, individual trajectories vary widely, along with quality of life and health-related quality of life.

Breathlessness is the most prominent symptom in advanced COPD and is the result of a complex interplay of physical, behavioural, psychological, contextual and spiritual/existential factors [15]. The concept of "total dyspnoea" has been proposed to reflect this [71], similar to the concept of "total pain" [72]. Enhanced understanding of the mechanisms of breathlessness in advanced COPD will help in the development of effective interventions.

Palliative treatments for COPD

Evidence of the benefits of interventions to treat symptoms and enhance quality of life in advanced COPD is sparse. Conducting trials in this population is fraught with challenges, but recently, advances have been made in overcoming these ethical, practical and methodological challenges [73].

Surgical and interventional treatments

Patients with upper lobe predominant emphysema and poor exercise tolerance should be referred for consideration of lung volume reduction surgery, as there is evidence of survival benefit as well as improvement in symptoms in this group of patients [14, 74]. There may be other groups who would not be fit for surgery but who may benefit from less invasive procedures, such as bronchoscopic approaches using coils, one-way valves, steam and biological agents, and who may gain relief from breathlessness and achieve enhanced quality of life [75]. Not all patients will want to undergo such procedures, particularly if the aim is palliative, and appropriate patient selection is as yet unclear. However, overestimation of risks by clinicians [76] and a lack of dedicated specialist regional COPD multidisciplinary teams [77] mean that patients who may wish to be entered into a clinical trial are not being offered this option.

Challenge: To improve coordination of COPD care and ensure patients, including those receiving a palliative care approach, are offered evidence-based interventions.

Table 4. Strength of evidence and grading of recommendations

Quality of evidence

- Grade A: Well-designed randomised controlled trials with consistent and directly applicable results
- Grade B: Randomised trials with limitations, including inconsistent results or major methodological weaknesses
- Grade C: Observational studies, and from generalisation from randomised trials in one group of patients to a different group of patients

Strength of recommendations

- Grade 1: Strong recommendation, with desirable effects clearly outweighing undesirable effects (or *vice versa*)
- Grade 2: Weak recommendation, with desirable effects closely balanced with undesirable effects

Recommendations (grade of recommendation in brackets (table 4)): Dedicated regional COPD multidisciplinary teams should be created, which may be virtual/teleconference/network teams. They should have expertise in COPD and specialist knowledge of patient selection for surgical and bronchoscopic techniques for emphysema treatment (2C).

Research needs: Research on appropriate patient selection for surgical and bronchoscopic interventions is needed. More long-term data is needed on quality of life, functional abilities, complications and survival post-procedure. Lessons should be learned from the palliative care literature in recruiting and maintaining patients in trials of palliative interventions.

Non-pharmacological interventions

There is evidence of a number of non-pharmacological interventions as treatments for dyspnoea; however, these interventions are not widely available to patients (table 5). The practicalities of administering such treatments, the acceptability to patients and the longer-term outcomes are as yet unproven. Further research is essential as many studies are underpowered, with inadequately described populations, a lack of standardised technique and terminology, and inconsistent outcome measures.

Challenge: To increase the availability and use of evidence-based non-pharmacological interventions.

Recommendations (grade of recommendation in brackets (table 4)): Patients with advanced COPD should have access to physiotherapy-led interventions, particularly strength exercises (1B), and to a lesser extent energy conservation and breathing retraining (2B). These could be delivered as part of a PR programme, but alternative models, including group and one-on-one sessions, should also be available. Patients should be advised of the benefits of walking aids and receive guidance on choice of the appropriate aid (2B). A hand-held fan should be offered to patients who are breathless but not hypoxaemic (2B). Other non-pharmacological interventions such as yoga, singing, cognitive behavioural therapy, progressive muscular relaxation, chest wall vibration, neuro-electrical muscle stimulation acupressure, acupuncture and mindfulness may be beneficial but there is currently insufficient evidence to recommend them (2C).

Table 5. Non-pharmacological interventions

First author/study group [ref.]	Intervention	Outcomes
Celli [15]	Smoking cessation (including nicotine replacement therapy, bupropion and motivational interviewing).	Patients at all stages, including advanced disease, benefit from stopping smoking. Whilst it may not be a priority for patients nearing the end of life, those with a prognosis of years must not be denied these treatments.
Puhan [78] **Lacasse [79]**	Strength exercise	Relieves breathlessness and fatigue, and enhances quality of life and sense of control, particularly as part of a PR programme. However, as COPD progresses, and particularly in the end-of-life phase, patients may not be able to participate in such programmes.
Velloso [80]	Energy conservation techniques, including pacing, rest periods during prolonged tasks, avoidance of bending and lifting, and adoption of specific postures.	No controlled studies examine these techniques. However, when using these techniques during activities of daily living, energy use was measurably lower in patients with moderate-to-severe COPD.
Dalton [81] **Probst [82]** **Solway [83]** **Honeyman [84]** **Gupta [85]**	Walking aids	Walking aids, including wheeled walkers and a rollator, improved breathlessness and increased 6MWT distance. Use may be limited due to patient perception.
Schwartzstein [86] **Booth [87]** **Galbraith [88]** **Bausewein [89]**	Hand-held fan (cool airflow stimulating nasal, pharyngeal and facial receptors of trigeminal nerve).	Hand-held fan may be a low-burden, inexpensive adjunct to treatment of dyspnoea in advanced COPD. Positive results have been found in both exercise-induced and chronic dyspnoea. This beneficial effect was not reproduced with longer follow-up.
Hochstetter [90] **Wu [91]** **Garrodl [92]** **Bausewein [93]**	Breathing training, including pursed-lip breathing. (A challenge to evaluate as techniques are insufficiently described and outcome measures are not standardised [94].)	Pursed-lip breathing allows increased expiratory time, increases vital capacity, reduces dynamic hyperinflation and improves gas exchange. Studies on pursed-lip breathing in addition to various other techniques, such as diaphragmatic breathing, positioning and panic management, have improved exercise tolerance in those able to undertake exercise.
Pomidori [95] **Donesky-Cuenco [96]** **Fulambarker [97]**	Yoga (may be a more sustainable way to deliver breathing training, with the potential additional benefits of strength training, anxiety reduction and socialising).	Although small studies have indicated that this may be an acceptable intervention and may improve quality of life, as measured using the SGRQ, there is inadequate evidence to recommend such interventions at present.
Lord [98]	Singing	RCT comparing a 6-week course of twice-weekly singing lessons to usual care in 28 patients showed improvements in anxiety and the physical component of the SF-36 but not measures of breathing control, functional exercise capacity or recovery time.

Continued

Table 5. Continued

First author/study group [ref.]	Intervention	Outcomes
Kunik [24] **Health Quality Ontario Group [99]** **Eiser [100]**	CBT	Six sessions of CBT resulted in sustained improvement in exercise tolerance in patients suffering from severe COPD and anxiety. In an RCT, a single 2-h session of group CBT and weekly calls for 6 weeks reduced both depressed mood and anxiety, but not physical functioning. Other studies have not reliably replicated these results.
Renfroe [101] **Lolak [102]**	PMR	PMR taught in one session every week for 4 weeks, followed by daily home practice with taped instructions, led to significant decreases in dyspnoea and anxiety in a small group of 12 patients with COPD within the sessions, but these outcomes were not sustained at 4 weeks. PMR may not have specific benefits over a PR programme.
Nakayama [103] **Fujie [104]** **Cristiano [105]**	Chest wall vibration	Three studies of patients with COPD involved attaching vibrators to the chest wall, which vibrated in-phase with the breathing cycle and led to decreased breathlessness. All studies were completed over a short period of time, on a single occasion and were conducted in the respiratory laboratory, limiting conclusions that can be drawn for practice.
Vivodtzev [106] **Neder [107]** **Bourjeily-Habr [108]**	NMES	NMES performed for 15–30 min on 3–5 days a week for 4–6 weeks led to improved breathlessness on CRQ, modified Borg scale and other measures. An increase in walking distance and BMI has also been found. The interventions were well tolerated.
Bausewein [93] **Bohlmeijer [109]** **Chan [110]**	Other: distractive auditory stimuli (music), acupuncture, acupressure, and mindfulness	There is a lack of evidence of benefit from distractive auditory stimuli (music), acupuncture or acupressure in advanced COPD. Although mindfulness practice has been shown to improve mental health in chronic disease with a small effect size, studies so far have failed to find evidence of benefit in patients with COPD. It may be challenging to demonstrate benefits from such therapies in trials but individual patients may feel they are beneficial.

SGRQ: St George's Respiratory Questionnaire; RCT: randomised controlled trial; SF-36: Short Form 36; CBT: cognitive behavioural therapy; PMR: progressive muscular relaxation; NMES: neuro-electrical muscle stimulation; CRQ: Chronic Respiratory Disease Questionnaire.

Research needs: Research on the short- and medium-term effects of non-pharmacological interventions is needed, as is consideration of the feasibility of delivery and acceptability to patients, particularly when considering chest wall vibration. Any new studies must be carefully designed to separate the generic effects of, for example, group activity, and the specific effects of interventions, such as singing or yoga.

Pharmacological interventions

Since there is no transition point from "disease-oriented" to palliative care in COPD, established treatments aimed at reducing bronchoconstriction and airway inflammation as advised in guidelines, should continue [14, 15]. In addition, such treatments are the first step towards symptom control, and so form a part of a palliative care approach. A combination of an inhaled long-acting anticholinergic, an inhaled long-acting β-agonist and an ICS can provide ongoing symptomatic relief and may reduce the frequency of exacerbations [111]. Additional pharmacological interventions become more appropriate as the disease progresses (table 6). There is a constant need to balance the benefits of additional medication against potential side-effects, interactions with other treatments, and the burden of polypharmacy for the patient and carer.

When considering whether to initiate pharmacological treatments for intractable breathlessness, the clinician should ensure optimal treatment with more established treatments. A dyspnoea ladder has been proposed by Rocker *et al.* [120] (figure 3), as a parallel to the WHO pain ladder, in order to facilitate appropriate step-wise escalation of therapy in all breathless patients, not just those at the end of life.

Many questions remain in relation to opioid use in COPD, as identified by Johnson *et al.* [150]. 1) Is relief of breathlessness a class effect, or are some opioids more effective than others? 2) Is it possible to identify subgroups of patients who are more likely to benefit? 3) Is there a role for alternative routes of administration, such as nebulised, intranasal or buccal? 4) By what mechanisms do opioids impact on the sensation of breathlessness and is this a predominantly central or peripheral effect? 5) Are there synergistic effects with other medications? 6) What are the barriers and facilitators to opioid prescribing in breathlessness? Similarly, questions remain regarding the safety and efficacy of benzodiazepines. Further studies are essential to identify patients who benefit, to explore adverse effects and to reassure prescribers.

Challenge: To use pharmacological interventions in advanced COPD safely, effectively and in a way that is acceptable to patients.

Recommendation (grade of recommendation in brackets (table 4)): Oral or parenteral opioids should be used to relieve breathlessness in advanced disease, starting with a low dose and titrating up (1B). Benzodiazepines should not be used to treat breathlessness in advanced COPD (1B). They can be considered for treatment of panic attacks but use should ideally not be regular (2C). Antidepressants are recommended for patients with COPD and anxiety and/or depression, with selective serotonin reuptake inhibitors as first-line treatment (1C). Beta-blockers are safe and should be given to patients with cardiovascular comorbidities, but are not first line for anxiety (2C). Stimulant drugs and busiprone are not recommended for use (2C). Long-term oxygen therapy should be provided for patients who are hyoxaemic but is not a treatment for breathlessness (1B). Individual assessments should be made to identify those who benefit from short-burst oxygen (2C).

Table 6. Pharmacological interventions

First author/study group [ref.]	Intervention	Outcomes
Edmonds [3] **Au [7]** **GOLD 2015 [16]** **Abernethy [112]** **Jennings [113]** **Bar-Or [114]** **Foral [115]** **Coyne [116]** **Charles [117]** **Robin [118]** **Young [119]**	Opioids. In practice in the UK, a common regime is to start with 0.5–2 mg oral morphine every 4–8 h and titrate up as tolerated, monitoring for side-effects [120].	Reflecting current evidence and practice, the 2015 update of the GOLD COPD guidelines recommends oral and parenteral opioids for treating dyspnoea in patients with severe disease. Concerns about possible respiratory depression are countered with evidence that at appropriate doses, there is no respiratory depression in patients with advanced COPD prescribed opioids. The most rigorous way to identify patients who benefit is through a RCT. Physicians continue to have concerns about the use of opioids in the medium-to-long term, in part related to concerns about addiction and respiratory depression that may not reflect current evidence. Pain is a common symptom in patients with COPD nearing the end of life and is currently under-recognised and under-treated. Evidence for nebulised opioids is limited due to the use of variable preparations and dosing schedules, but randomised studies continue to fail to show benefit.
Simon [121] **Edmonds [3]** **Murciano [122]** **Ekstrom [123]** **Vozoris [124]**	Benzodiazepines. Both anxiety and insomnia are common and impair quality of life in COPD, and benzodiazepines improve sleep duration and quality, and do not lead to nocturnal hypoxaemia or apnoeas.	A Cochrane review concluded that there was no evidence of a beneficial effect of benzodiazepines in the relief of breathlessness in advanced COPD or cancer. However, the authors suggested considering benzodiazepines as second- or third-line treatment for breathlessness, and also for breathlessness with panic attacks. Safety concerns remain. A large, prospective, longitudinal cohort study of patients starting LTOT for COPD found that benzodiazepine use was not associated with increased admissions, but was associated with a modest increase in mortality with a dose–response trend. A recent retrospective population-based cohort study found a significantly higher risk of outpatient respiratory exacerbations and emergency department visits for COPD or pneumonia within 30 days of new benzodiazepine prescription, but not hospitalisation, ICU admission or mortality.
Borson [125] **Yellowlees [126]** **Mikkelsen [127]** **Taylor [128]** **Smoller [129]** **Lacasse [130]** **Eiser [131]** **Radruch [132]**	Antidepressants. In moderate-to-severe COPD, prevalence rates of anxiety and depression are 20–50% and up to 90% for either or both [5, 6, 24]. They are undertreated [24] despite evidence that treatment leads to improvements in the physical, psychological and functional state of the patient [125, 127].	Both SSRIs and TCAs have been found to improve anxiety and depression in patients with COPD. It has been suggested that newer generation antidepressants should be used, due to theoretical benefits in side-effect profile, and SSRIs are suggested as the first choice due to greater evidence of enhanced quality of life in depression in the context of chronic physical health problems. Both sertraline and paroxetine have shown beneficial effects in patients with COPD but extended treatment duration may be required to show such benefit.
Radbruch [132]	Stimulant drugs, including modafinil, pemoline and donepezil.	Stimulant drugs have been used to treat fatigue, but even in malignant disease, controversy about their use exists. There is insufficient evidence to recommend such drugs in non-malignant disease, including COPD.

Continued

Table 6. Continued

First author/study group [ref.]	Intervention	Outcomes
Argyropoulou [133] **Singh [134]**	Busiprone, a partial 5HT1A receptor agonist.	Busiprone gained interest as a respiratory stimulant and anxiolytic. However, positive effects on anxiety have not been replicated in a subsequent RCT.
Albouiani [135] **Quint [136]**	Beta-blockers have an anxiolytic effect but are often avoided in COPD due to concerns about bronchoconstriction.	There is increasing evidence that beta-blockers are safe, reduce cardiovascular mortality and may have other benefits. We are not aware of any trials using beta-blockers for anxiety in COPD, but if it is felt to be beneficial, they should not be denied this due to concerns about side-effects. They should be started at a low dose and titrated up.
Booth [87] **Eaton [137]** **Booth [138]** **Bruera [139]**	LTOT and SBOT	LTOT is a well-established treatment for patients with severe hypoxaemia (P_{aO_2} <7.3 kPa) for whom it improves survival and quality of life [140, 141]. It is not effective for those with moderate hypoxaemia (P_{aO_2} 7.4–8.7 kPa) without cor pulmonale and there is no evidence for the use of LTOT in patients who are breathless but not hypoxaemic [142, 143]. However, some patients who do not meet criteria for LTOT benefit from SBOT and can be identified through RCTs. Oxygen therapy can have a number of unintended adverse consequences, including psychological dependence, restricted activities, impairments in communication, perceived social stigma and increased social isolation.
Hui [144]	High-flow oxygen (interesting because possible advantages over low-flow oxygen include improved mechanics and associated decreased metabolic cost of breathing).	In a small study in cancer patients with persistent dyspnoea, high-flow oxygen (delivering ≤40 $L \cdot min^{-1}$ of humidified heated oxygen through a nasal cannula) was associated with an improvement in dyspnoea to a similar degree to NIV. 33% of all patients in the trial had COPD and there were no adverse effects reported. There are concerns about using 100% oxygen (as in this trial) in patients with hypercapnic respiratory failure but modifications to the protocol would be possible, utilising the high-flow element at a lower F_{IO_2}. This was a feasibility study and we await the results of a planned RCT with interest.
Celli [15] **Wijskra [145]** **Clini [146]** **Kolodziej [147]** **Lloyd-Owen [148]** **Struik [149]**	NIV	NIV is an established treatment for acute respiratory failure but its place in chronic respiratory failure in COPD is less clear. There is a wide variation of practice across Europe and conflicting outcomes from trials. Some trials have suggested a benefit in quality of life in some patients with stable chronic respiratory failure in COPD. The most recent Cochrane review concluded that there was no consistent clinically or statistically significant effect on gas exchange, exercise tolerance, health-related quality of life, lung function, respiratory muscle strength or sleep efficiency [149].

GOLD: Global Initiative for Chronic Obstructive Lung Disease; RCT: randomised controlled trial; LTOT: long-term oxygen therapy; ICU: intensive care unit; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants; SBOT: short-burst oxygen therapy; P_{aO_2}: arterial oxygen tension; NIV: noninvasive ventilation; F_{IO_2}: inspiratory oxygen fraction.

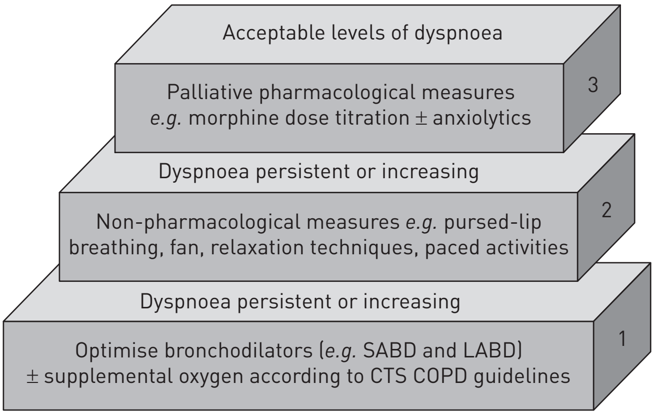
Acceptable levels of dyspnoea
Palliative pharmacological measures
e.g. morphine dose titration ± anxiolytics
3
Dyspnoea persistent or increasing
Non-pharmacological measures *e.g.* pursed-lip breathing, fan, relaxation techniques, paced activities
2
Dyspnoea persistent or increasing
Optimise bronchodilators (*e.g.* SABD and LABD)
± supplemental oxygen according to CTS COPD guidelines
1

Figure 3. The dyspnoea ladder. SABD: short-acting bronchodilator; LABD: long-acting bronchodilator; CTS: Canadian Thoracic Society. Reproduced and modified from [120] with permission from the publisher.

Research needs: Larger studies are needed in the use of opioids for breathlessness, and benzodiazepines for anxiety or panic disorder, focussing on patient identification, safety, adverse effects, and patient and clinician perceptions of use. Larger studies are needed on effective ways of screening for anxiety and depression, initiating antidepressants and examining relevant outcomes such as quality of life. New treatments for breathlessness are needed, and interventions such as high-flow oxygen, which have a physiological basis, need to be tested in clinical trials to assess efficacy and acceptability.

Information needs of patients and carers, and communication

Guidelines suggest that patients with at least moderate COPD should have attended a PR programme [14, 15], including patient information sessions. However, multiple studies show that patients with COPD and their carers feel there is inadequate education and information provided, particularly as the disease progresses [5, 151]. Several focus group participants described the moment they learned that COPD was "terminal", "incurable" or "fatal" and expressed surprise at this fact. There is much less public understanding of COPD as a disease, compared to other life-limiting conditions, which may contribute to this. In addition, EDMONDS *et al.* [3] found that only 62% of patients who died in the following 12 months knew they were dying, and only 8% had been told this by a hospital doctor. CURTIS *et al.* [151] identified specific areas of information need: diagnosis and disease process; treatment; prognosis; what dying might be like; and advance care planning. Similarly, carers have unmet information needs, particularly around the trajectory of illness and the dying process, which contribute to anxiety and impaired quality of life [11, 12]. Models of palliative care in COPD must integrate the education of patients and carers as part of the therapeutic relationship.

Advance care planning

Advance care planning is a structured discussion between healthcare professionals and patients and their families or carers about their wishes and thoughts for the future. The process of advance care planning may lead to completion of a number of documents, which formally state these wishes and have legal standing (table 7).

Table 7. Types of advanced care planning documents used in the UK

Document	Aims
Advance Statement of Preferences	Sets out an individual's priorities and preferences
Advance Directive to Refuse Treatment	States specific medical treatments the patient does not want to receive and clarifies the context in which this would be the case
Lasting Power of Attorney	Nominates someone to speak on the patient's behalf should they lose the capacity to make healthcare-related decisions

These documents take various forms in other European countries and are often known as living wills and healthcare proxys [152]. Not all patients will complete all documents, and many will only wish to complete an Advance Statement (AS). ASs and Advance Directives to Refuse Treatment have been criticised as not changing end-of-life decision-making [153], but a randomised controlled trial in elderly patients had many positive outcomes: patients' end of life wishes were more likely to be known and followed; family members had less stress, anxiety and depression; and patient and family satisfaction with care was higher [154]. The documents themselves are only part of the process; it is the high-quality, honest communication that occurs between the healthcare team, patient and family/carer that has impact.

The value of advance care planning is that preferences are documented in advance, to pre-empt a situation in which a patient has lost the capacity to make decisions or communicate those decisions. Heffner *et al.* [155] found that 99% of 105 patients with COPD in a PR programme wished to discuss prognosis and advance directives, but only 20% had these discussions. Knauft *et al.* [156] identified a number of barriers and facilitators to end-of-life care discussions but concluded that no generalisations could be made, and the specific factors that helped or hindered such discussions were dependent on individual patient–physician pairs. The most commonly cited barriers from patients were a wish to concentrate on being alive and concerns about continuity of care at the end-of-life.

The possibility that they may destroy hope is a concern for physicians. However, a study in 19 patients with end-stage renal disease demonstrated that facilitated advance care planning can positively enhance rather than diminish patients' hope [157]. Interestingly, factors that sustained patients' ability to hope were: more information earlier in the course of the illness focussing on the impact on daily life; empowerment of the patient; and enhancing professional and personal relationships. The reliance on health professionals to initiate end-of-life discussions and the daily focus of clinical care were seen as potential barriers to hope. A model of "hoping for the best but preparing for the worst" is now established as a framework for advance care planning discussions [158].

Physicians find it challenging to know when is the right time to discuss intubation, ventilation and ceilings of care with patients. In one study, a majority felt that the optimal time was when the patient was stable, but more often the discussion occurred during an acute exacerbation, a time of crisis. Patients with life-limiting illness who wish to discuss their preferences for end-of-life care, wish to do so relatively early in the course of the illness but often do not get the opportunity [159]. Physicians have emphasised the need to know the patient, in order to understand their perceptions of their quality of life and expectations of treatment. Previous studies have shown that physician perception of quality of life is a major factor in considering whether they believe intubation would be in the best interest of a patient [44] but physicians' assessments of patients' quality of life do not necessarily match patient perceptions [160]. If discussions about treatment preferences do not take place, then at a time of exacerbation the physician has to make a "best-interests" decision regarding intubation. This will integrate the views of the physician themselves and family members of the patient. Importantly, the preferences of patients regarding such interventions cannot be predicted from markers such as FEV_1 % pred, breathlessness or age, making advance care planning essential to ensure patient wishes are respected.

Preferred place of care is one area commonly discussed as part of advance care planning and is under-researched in COPD. In the study by EDMONDS *et al.* [3], 72% of patients with COPD died in a hospital, compared to 51% of patients with lung cancer, and 12% patients died at home, compared to 27% of those with lung cancer. Breathlessness is a frightening symptom, associated with intense acute anxiety. It may be that hospital feels like a place of safety and is therefore preferable to home as a final place of care for a larger proportion of patients with COPD than other conditions.

There will always be some patients who do not wish to contemplate or discuss the future. Such a choice must be respected. Discussions about prognosis and treatment preferences must always be patient-centred, with information being given at a pace and a level of detail that matches the patient's wishes. This can be challenging if the patient does not wish to discuss the future, but their family or carer has unmet information needs.

Challenge: To improve communication in advanced COPD.

Recommendation (grade of recommendation in brackets (table 4)): Patients with COPD and their relatives need more information at all stages of the disease. Conversations about prognosis, expectations and advance care planning should be integrated into routine care at an earlier stage in the disease (2C). Training in shared decision-making and advanced communication skills are needed for respiratory physicians who undertake this work.

Research needs: Further studies on factors which facilitate or hinder advance care planning for patients, relatives and physicians are needed in order to design services in which such conversations are at the centre of care. Research into preferred place of care in COPD is essential.

Models of care

Currently, patients with COPD are most likely to be cared for in a reactive crisis model at the time of deterioration, with management focussed exclusively on prolongation of life [4, 7]. Patients are often "invisible" until they have an exacerbation, with inadequate attention being paid to their daily symptom burden, and the social and psychological care needs of patients and carers. Care is often fragmented with poor information flow between primary and secondary care, and there is a lack of continuity and forward planning, which are of importance to patients [67, 161]. It has been highlighted that a tendency towards "either/or" thinking in advancing chronic illness contributes to fragmentation [162]. There is disagreement as to the roles and responsibilities of the different healthcare professionals involved in the care of patients with severe COPD, particularly in relation to who should initiate advance care planning discussions [163]. Too often this leads to no one taking the initiative.

Table 8. Models of care

First author [ref.]	Intervention	Model	Outcomes
Higginson [30] **Booth [165]** **Booth [169]** **Farquhar [170]** **Farquhar [171]**	Breathlessness Intervention Service, run by a palliative care consultant, specialist physiotherapist and occupational therapist in Cambridge, UK.	A time-limited specialist service for patients with intractable breathlessness regardless of primary diagnosis. Runs alongside usual care by general practitioners, and respiratory or oncology specialist teams. It is a flexible model but generally comprises four sessions, at least one of which is a phone call. Interventions include: education for patient and carer; individualised exercise programme and energy conservation techniques; hand-held fan; mindfulness techniques; and referral to other specialist services including hospice day centre and PR.	A randomised controlled, parallel group, pragmatic, single-blind, fast-track trial of a breathlessness support service (modified from the BIS and integrating respiratory medicine specialists into the service) reported a significant improvement in "breathlessness mastery" at 6 weeks, compared to controls. Improved confidence, function and control over breathlessness. No increase in costs of care. Survival was better in the group receiving early breathlessness support service, for patients with non-cancer, including COPD. Survival was a secondary end-point and this outcome requires further investigation.
Rocker [166] **Young [172]** **Horton [173]**	The INSPIRED programme in Canada.	Identified patients during hospital admissions who were then enrolled in a structured programme of case management by a "respiratory therapist educator", supported by a respiratory physician with expertise in advanced COPD, and a "spiritual care practitioner" to support advance care planning. Components included: a modular educational programme; a comprehensive palliative care assessment with goal-setting; an individualised management plan, including referral to specialist services; shared documentation across teams; and follow-up by phone and home visits for 4 months.	Initial evaluation (presented at the ATS conference in 2012) showed a 70% reduction in hospital emergency visits, admissions and length of stay in the 6 months following the programme compared to the year before, with a saving of US$487 000. As yet, there has been no article describing the evaluation or outcomes in more detail. The same group has conducted a faesability study of a modified version of the programme, with patients identified from outpatient clinics. An evaluation and preferably an RCT would be welcomed.
Ortiz [174] **Reid [175]**	PCMH, a primary care-based model, piloted in California, USA. Extends the principles of the chronic care model.	Multidisciplinary team care focussed on maintaining wellness rather than merely reacting to acute illness. Physician assistants and/or nurse practitioners provided most first-contact care, and physicians led the care team and managed complex patients. Investment and changes in practice were necessary to achieve the model:	A 12-month quasi-experimental study comparing a designated PCMH practice with usual care clinics found 29% fewer urgent care visits and 11% fewer hospitalisations for ambulatory care sensitive conditions (including COPD) than usual care patients. Staff burnout levels were reduced, and quality indicators improved significantly.

Continued

Table 8. Continued

First author [ref.]	Intervention	Model	Outcomes
		clinicians' caseloads were reduced, duration of standard visits were increased, provided, and the staff mix was altered.	However, overall costs were unchanged. Larger studies with longer follow-up would be helpful.
Skilbeck [4] **Gore [5]** **Booth [87]**	No specific studies but specialist respiratory nurse input was highlighted as a component in many proposed models.	Respiratory nurse specialists providing coordination and continuity of care, and facilitating access to multi-professional specialist advice.	Respiratory nurse input increases patient satisfaction, but studies have failed to show impact on quality of life or reduction in hospital admissions.
Gardiner [168] **Martinez-Gonzales [176]**	In-home palliative care.	Other coordinated care models included in a systematic review and meta-analysis of integrated care programmes.	In-home palliative care for those with a predicted prognosis of <1 year increased patient satisfaction and reduced costs in a group that included patients with COPD in Hawaii, USA. A systematic review and meta-analysis of integrated care programmes in chronically ill patients included seven reviews in COPD. Studies and reviews were of mixed quality. Organisational culture, governance structure and financial management were rarely assessed.
Smith [177] **Bomba [178]**	EPaCCS have the potential to facilitate teamwork across boundaries of space, time and discipline [179]. To date, shared-care or integrated-care programmes have made little use of information technology [180].	Recently, EPaCCS have been implemented in New York, USA (electronic medical orders for life-sustaining treatment or eMOLST), and London, UK (CMC).	Provisional reports suggest that use of an EPaCCS increases the number of patients dying in their preferred place of care. However, any improvements are likely to be multifactorial. Other outcomes such as improved quality of life are as yet unproven. In addition, only a small proportion of the target population is covered by EPaCC projects and not all healthcare providers are aware of the projects.

BIS: Breathlessness Intervention Service; INSPIRED: Implementing a Novel and Supportive Program of Individualised Care for Patients and Families Living with Respiratory Disease; ATS: American Thoracic Society; RCT: randomised controlled trial; PCMH: Patient-Centred Medical Home; EPaCCS: Electronic Palliative Care Co-ordination Systems; eMOLST: electronic Medical Orders for Life-Sustaining Treatment; CMC: Coordinate My Care.

In recognition of these deficiencies, a number of new models of care have been proposed and some have been piloted [30, 164–166]. They follow the model of mixed management [167] and simultaneous care [168], such that respiratory and palliative care services work in parallel, and "active" treatments are provided alongside a palliative care approach. Although we are aware of innovative practice in individual institutions, not all of these have been formally evaluated, and therefore the available literature is limited. A number of examples are given in table 8.

Unanswered questions abound in relation to models of care for optimal delivery of a palliative care approach to patients with COPD. What are the outcomes that matter in evaluating models of care? Which models work in which contexts and how can commissioners and providers shape systems to meet the needs of local communities? What is the role of the hospice and how and when should this be introduced? How can the activity of inter-professional teams be captured and reimbursed, to ensure sustainable funding for services? How can other aspects of holistic care and advocacy, such as access to benefits advice, be integrated into the model? How can the patient and carer be included in the interdisciplinary team in a meaningful way, which utilises their expertise without being burdensome? There is an urgent need to invest in the evaluation of existing programmes and to embed research in programme development in order to meet the needs of patients with COPD and their carers in the future.

Challenge: To define and encourage as standard, good models of care, which include enhanced working between primary and secondary care, and between palliative and respiratory specialists, with patient needs driving service design

Recommendation: The experience and outcomes from different models of care should be shared within the respiratory and palliative care communities, with research built into newly established models of care.

Research needs: There is very little research on what constitutes a good model of care, and studies on all aspects of this question are urgently needed.

Conclusion

Patients with advanced COPD have a high burden of symptoms and significant physical, emotional and psychological needs. These are not being met by current models of care, leaving patients with impaired quality of life and a lack of advance care planning. A palliative approach to care would benefit many of these patients, in parallel with an "active" treatment approach. More accurate prognostication would be welcomed by healthcare professionals, patients and carers. In addition, investment in research into interventions for breathlessness and other symptoms such as pain, fatigue, anxiety and depression is essential. There are great opportunities to improve the lives of patients with advanced COPD, which can be achieved if respiratory and palliative care specialists work in parallel to conduct research and to support patients and their carers.

Proposed treatment plan for patient in case vignette:

A case-conference is arranged, inviting the patient, her daughter, members of the palliative care team and the respiratory team, an occupational therapist and a physiotherapist. Consideration is given to inviting a social worker and the patient's GP. The discussion addresses the patient's and her daughter's information needs, and establishes clear ceilings of treatment, plans for when she deteriorates; who to contact and what interventions to use and when. A clear explanation of the rationale for the use of morphine in breathlessness is given, with reassurance regarding potential side-effects. A plan is made for a trial of low-dose morphine. The priorities and preferred place of care of the patient are established. The outcome of the meeting is clearly documented, with information being shared across primary and secondary care. Plans for community follow-up are confirmed. Information is entered onto an electronic palliative care coordination system.

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